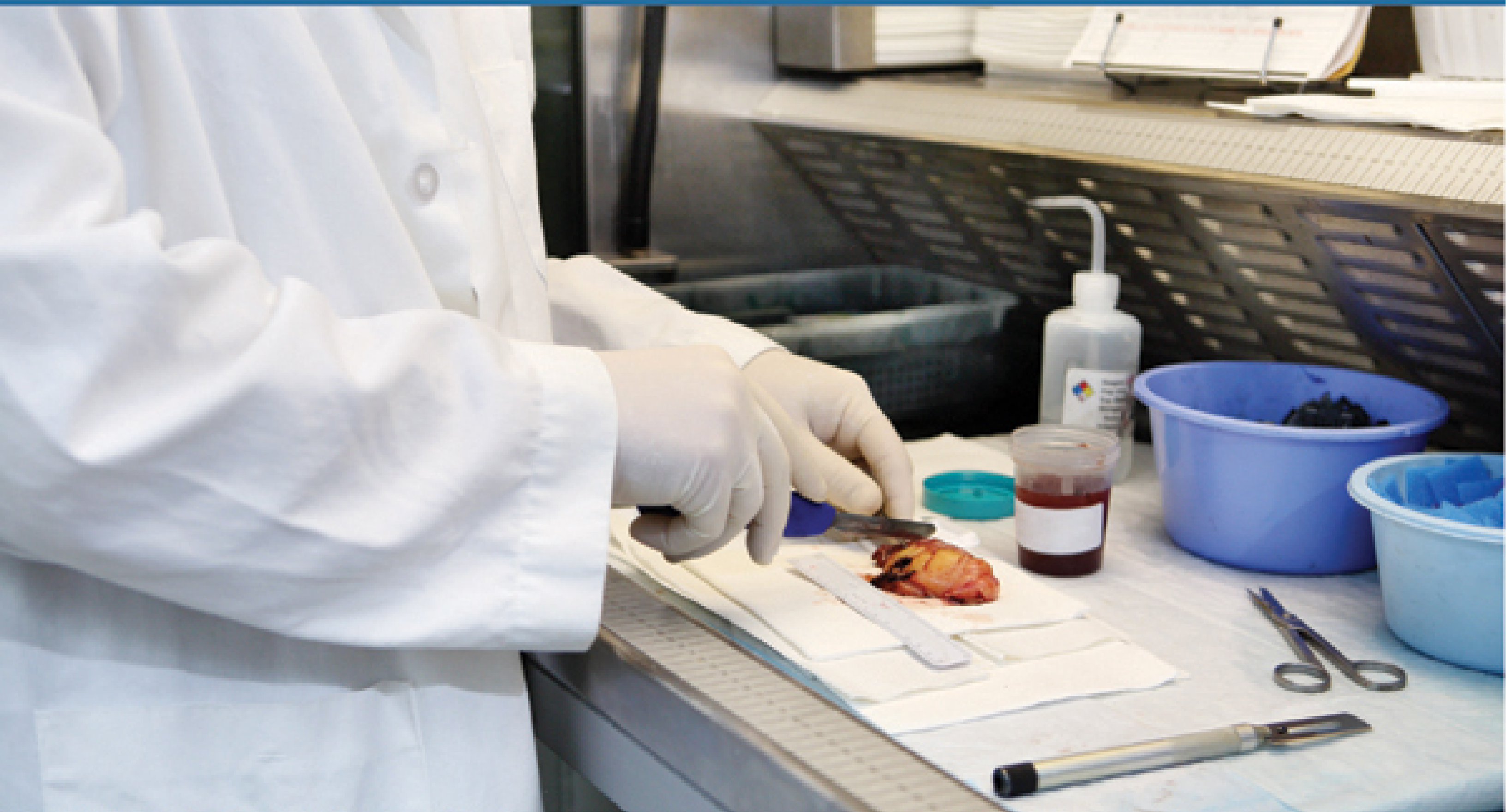
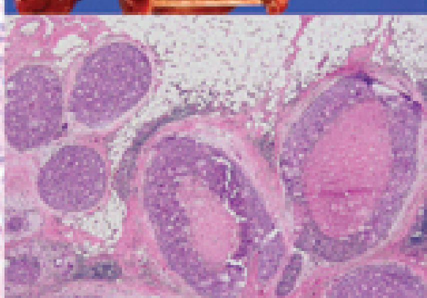
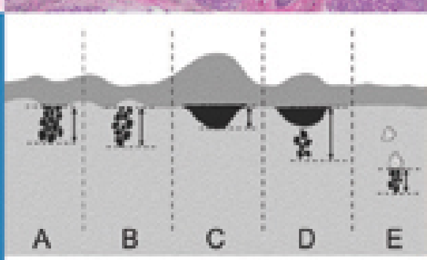
Grossing, Staging, and Reporting



An Integrated Manual of Modern Surgical Pathology

Qihui 'Jim' Zhai





COLLEGE of AMERICAN PATHOLOGISTS

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College of American Pathologists
325 Waukegan Road
Northfield, Illinois 60093
800-323-4040
cap.org

Contents

Contributors

Editor

Qihui "Jim" Zhai, MD
Mayo Clinic Florida
Jacksonville, FL

Contributing authors

Volkan Adsay, MD
Koc Universitesi Hastanesi and KUTTAM Research Center
Istanbul, Turkey

Sylvia L. Asa, MD, PhD
University Hospitals Cleveland Medical Center
And University Health Network, Toronto
Case Western Reserve University

Diana Bell, MD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Marilyn M. Bui, MD, PhD
Moffitt Cancer Center
Tampa, FL

Natalia Buza, MD
Yale University
New Haven, CT

Shelley Caltharp, MD
Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, GA

Patricia Chévez-Barrios, MD
Houston Methodist Hospital
Houston, TX

Mark A. Cappel, MD
Gulf Coast Dermatopathology Laboratory
Tampa, FL

Mathieu C. Castonguay, MD
Dalhousie University
Halifax, NS

Deyali Chatterjee, MD
Washington University School of Medicine
St. Louis, MO

Qingqing Ding, MD, PhD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Ahmet Dogan, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, NY

Ashwini K Esnakula, MD
University of Florida
Gainesville, FL

Fang Fan, MD, PhD
City of Hope Medical Center
Duarte, CA

Wai Chin Foo, MD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Ruifeng Guo, MD, PhD
Mayo Clinic
Rochester Rochester, MN

Jian He, MD, PhD
Medical College of Wisconsin
Milwaukee, WI

Pei Hui, MD, PhD
Yale University
New Haven, CT

Evita Henderson-Jackson, MD
Moffitt Cancer Center
Tampa, FL

Mark E. Jentoft, MD
Mayo Clinic Florida
Jacksonville, FL

Murli Krishna, MD
Mayo Clinic Florida
Jacksonville, FL

Brandon T. Larsen, MD, PhD
Mayo Clinic Arizona
Scottsdale, AZ

Li Liang, MD, PhD
Goshen Health
Goshen, IN

Xiuli Liu, MD, PhD
University of Florida
Gainesville, FL

Dylan V. Miller, MD
Intermountain Medical Center
Salt Lake City, UT

Matthew T. Olson, MD
Mayo Clinic Florida

Jacksonville, FL

Khela R. Pursell, PA(ASCP)
Mayo Clinic Florida
Jacksonville, FL

Xiaohua Qian, MD, PhD
Stanford University
Stanford, CA

Beverly Rogers, MD
Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, GA

Heather Rytting, MD
Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, GA

Rashmi Samdani, MD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Inga-Marie Schaefer, MD
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Sasan Setoodeh, MD
University of Texas Southwestern Medical Center
Dallas, TX

Melissa W. Taggart, MD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Laura H. Tang, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, NY

Huamin Wang, MD, PhD
The University of Texas
MD Anderson Cancer Center
Houston, TX

Paul Wawryko, MD
University of Manitoba
Winnipeg, MB

Shi Wei, MD, PhD
University of Alabama at Birmingham
Birmingham, AL

Wenbin Xiao, MD, PhD
Memorial Sloan Kettering Cancer Center

New York, NY

Hong Yin, MD
Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, GA

Yaxia Zhang, MD, PhD
Hospital for Special Surgery
New York, NY

Ming Zhou, MD, PhD
University of Texas Southwestern Medical Center
Dallas, TX

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CAP President, Dr. Patrick Godbey, graciously wrote the Foreword of this book. Thank you for your kind words and longterm support!

Mom and dad, thank you for being the amazing role models. Your lifelong love, support, and guidance has paved the way for me!

I wanted to thank my wife Jenny and our daughter Jasmine for putting up with me during this and the many other projects I spend time on. Your love and support has been an anchor and what allows me to continue to succeed in my career.

Qihui "Jim" Zhai

Foreword

As surgical pathologists, we must be able to gross specimens effectively, stage tumors accurately, and release comprehensive and succinct pathology reports in a timely fashion. Having a user-friendly hands-on guide for grossing, staging, and reporting available in gross rooms, sign-out areas, and pathologists' offices can aid in fulfilling this need.

Dr. Qihui "Jim" Zhai, an excellent surgical pathologist himself, has been aware of the growing need for such a hands-on guide. He has spent an enormous amount of time, with the assistance from the College of American Pathologists (CAP), creating extensive content and collaborating with extremely talented contributors from many different practices. Through these efforts, he has succeeded in a massive undertaking to create *Grossing, Staging, and Reporting: An Integrated Manual of Modern Surgical Pathology,* thus turning his vision into reality. This manual provides an innovative approach to integrating the critical components of grossing, staging, and reporting into organ-based chapters.

To our knowledge, this is the first book of its kind available to the pathology community that integrates all three essential components of modern surgical pathology into one comprehensive text. The chapters are organized by organ, with nearly every organ represented, and correspond to the CAP cancer protocol templates and the AJCC Cancer Staging Manual 8th Edition. The most recent version of staging of the cervix uteri (Version 9) has also been integrated.

The CAP has been promoting the idea of "standard practice" for years. Our Cancer templates, which are accessible to all, exemplify this idea. One of our CAP missions is to offer practical and valuable tools to our pathologists who directly take care of the patients. Quality of patient care is paramount. This book will be an invaluable resource to our daily practice by improving consistency, efficiency, and safety while shortening the turnaround time. This manual may not be limited to the pathology community; our clinical colleagues who treat cancer patients such as surgeons, radiation oncologists, and medical oncologists will likely also find this manual highly valuable.

The skills and techniques of grossing, staging, and reporting are traditional skills that all pathologists use on a daily basis. New molecular and genetic tools are fascinating and have resulted in many new diagnostic and therapeutic biomarkers that improve patient care. However, the significance and accuracy of molecular findings depends heavily on the consistent and accurate staging and clinical validation. It is this integration of the traditional skills (grossing, staging, and reporting) with the evolving molecular techniques that will allow us to offer standardized and individualized therapeutic regimens to patients with complex diseases.

The "Paragraph System" to describe the gross pathology of specimens is well-organized and is meant to significantly enhance the consistency among our reports from different institutions. Subsequently, it will facilitate communication amongst pathologists, including the consultation services for second opinions and transfer of care. Ultimately, our clinical colleagues and patients will benefit from these endeavors, and the consistency of pathology reports by different institutions will help them understand the pertinent information without difficulty. This book focuses on traditional skills such as how to gross and stage a surgical specimen as well as incorporation of molecular knowledge in select diagnostic entities. The authors have been creative in their approach in presenting these different (but related) aspects of the disease seamlessly. CAP Publications deserves a sincere "congratulations" for publishing this timely and high-quality book.

The CAP wants to thank Dr. Zhai and all the contributors for their passion, talents, dedication, and donation of their time to this vital manual. We are confident that this book will positively and profoundly impact the practice of surgical pathology and, ultimately, the quality of patient care in America and beyond.

Patrick Godbey, MD, FCAP President, College of American Pathologists

Preface

It is an honor and one of the highlights of my career (and of my life) to be intimately involved with this project, *Grossing, Staging, and Reporting: An Integrated Manual of Modern Surgical Pathology,* through collaboration with some of the most dedicated and talented pathology colleagues from various practice settings. The goal of this manual is to offer practical tips and updates for handling a resection specimen, from grossing to reporting, for practicing pathologists, trainees, and pathologists' assistants alike.

During my residency training at Mayo Clinic in Rochester, Minnesota, residents participated in a monthly gross conference with microscopic correlation called the "MBD" (so named for Dr. Malcolm B. Dockerty, a pioneer pathologist at Mayo Clinic). This conference was taught by the legendary Dr. Krishnan Unni and began with a gross photo for which every resident was called to offer a diagnosis. Once all the residents had given their opinion, the corresponding microscopic images would be correlated, and a diagnosis rendered. This conference was both "stressful" and fun for a junior resident. Nowadays, I benefit a great deal from my macroscopic diagnostic skills gained from this conference as I still go to evaluate gross specimens and advise where to sample during frozen sections and difficult cases.

After residency, I continued my training in an oncologic surgical pathology fellowship at the MD Anderson Cancer Center in Houston, Texas. While I was there, I grossed many complex specimens which enabled me to continue learning, improving upon the skillset acquired during residency. The Raymond's Paragraph System, a gross pathology report formatting system used to describe a particular specimen for most organ systems, was introduced by Dr. Kevin Raymond and then continued to be applied at Houston Methodist Hospital. Ms. Annette Dayton, an outstanding pathologists' assistant, along with Drs. Ayala, Ro, Schwartz, and Raymond, summarized their experience and published the manuscript, "Paragraph System: An Alternative Format for the Organization of Gross Pathology Reports and Its Implementation in an Academic Teaching Hospital," in *Archives of Pathology & Laboratory Medicine* in 2009.

Training and practicing in different settings granted me the opportunity to read pathology reports from all over the world. The styles and approaches to gross pathology vary quite drastically. Sometimes, it can be difficult to mentally reconstruct the specimen based on the original gross description, which may make it impossible to evaluate and stage the tumor accurately.

The importance of consistency and standard approaches to (1) handling the specimen, (2) staging the tumor accurately, and (3) reporting comprehensively (but succinctly) cannot be over-emphasized. The quality of our practice in pathology directly determines the safety and quality of the patients' care. The College of American Pathologists (CAP) has been continuously working to promote this concept. This book is an example that can aid in "standard practice" among our fellow pathologists.

Molecular and genomic tools have become vital in modern pathology and have empowered us to resolve many mysteries of the past. In particular, biomarkers have allowed us to more accurately classify tumors, offer therapeutic choices, and predict prognosis. Validation of these powerful tools depends heavily on reliable clinical staging information. Therefore, the traditional grossing, staging, and reporting skills will serve an even more vital role as the foundation for future individualized regimens for cancer patients. This book is unique in that it is the first manual discussing all three major surgical pathology components (grossing, staging, and reporting) within a single manual.

Grossing: How one grosses a resection specimen directly determines what the pathologist can see on the glass slides, staging information, and the turnaround time report sign-out. We need to keep these in mind while we dissect the specimen. Step-by-step and illustrative procedures are used to obtain the tissue blocks that are critical to the microscopic examination and are the foundation of the comprehensive report. We should be cognizant of the economy of the laboratory and practice. Sampling and processing sufficient blocks, while not oversampling, is essential for the subsequent staging information. Typical gross photos are demonstrated in

many chapters, and self-explanatory illustrations are presented. We have emphasized the standard way to handle a resection specimen using the paragraph system with five paragraphs.

Paragraph 1 lists organs in the specimen with the overall measurements and weights.

Paragraph 2 describes the main/primary pathology of the specimen, including the size, location, characteristics, extent of disease, and margins.

Paragraph 3 describes the secondary pathology.

Paragraph 4 lists the colors of ink and their designation.

Paragraph 5 lists the block labeling and specific description.

A sample gross pathology description is provided for each organ and can be adapted and individualized for the needs of each laboratory.

Staging: How to stage a tumor accurately by recognizing common pitfalls and solutions to avoid them is critical skill needed to precisely describe extent of disease. Some chapters contain pertinent microscopic photos to illustrate staging dilemmas and how to solve them. This manual provides a standard approach to staging based on the *AJCC Cancer Staging Manual,* 8th Edition. In the future, the AJCC will not publish a manual to contain all the recent changes as it may not reflect timely developments. Instead, each year, a new version of several organs may be released with the most significant updates. Version 9 of the AJCC cancer staging manual for cervix uteri is integrated into this text.

Reporting: How to formulate a "standard" pathology report to share our findings, and be used for future treatment and prognosis, is the final product of the process. This report will be a medical and legal document and should include all the necessary information while remaining succinct. The materials from the CAP cancer protocol templates are an invaluable resource. Our authors took advantage of this resource by using some of the critical information found within them. We by no means request you to strictly follow our samples, understanding the difference in style and respecting the many ways of expression. A critical aspect to our daily practice is maintaining efficiency. Reports that are long and that contain unnecessary information could lead to more time spent typing, editing, and proof-reading instead of other important tasks.

In this manual, the authors emphasize the traditional skills used in our daily surgical pathology practice and include pertinent molecular knowledge that has become standard in modern surgical pathology. More than 40 esteemed authors from different practice settings contributed to this book; inevitably, the styles will vary slightly here and there; however, the critical information and essential points are focused. It is our collective goal that pathologists, trainees, and pathologists' assistants will find this manual a valuable tool and resource for grossing, staging, and reporting in their daily practice.

Qihui "Jim" Zhai, MD, FCAP

The Perfect Cut: Focusing on Safety to Achieve Quality in Grossing Technique

Matthew T. Olson, MD

Safety is a critical dimension to every laboratory endeavor, but rarely is it more acute and more overlooked on a daily basis than in the grossing room. The underappreciation of safety in grossing rooms is usually tacit. New prosectors may be told to follow the three-word rule, "don't cut yourself," or the five-word rule, "never let your guard down." While there certainly is a need for personal vigilance, these directives are a missed opportunity to address what makes a grossing technique safe or unsafe. The impact of safety on the grossing workforce is elementary: a prosector cannot be effective on the job if he or she is repeatedly in treatment for workplace injuries. An equally compelling argument for safety—and the central thesis of this chapter—is that safe practices raise the quality of grossing. Quality in grossing raises the smoothness of cuts and, by extension, the quality of the histology. This in turn makes the pathologist's job at the microscope easier and improves patient care. When a prosector is comfortable at the station, has the correct tools in ideal locations, controls the items on the cutting board, and only cuts when the specimen is secure, the cuts made will be straighter, the cut surfaces cleaner, and the work more efficient.

Sharps safety and systems-based practice

Clinical laboratories that receive highly standardized specimens such as vials of blood can develop written policy manuals that dictate an operator's every movement. In contrast, gross laboratories receive variegated specimens that frequently require a tailored approach. Unsurprisingly, in many grossing labs, individual practices arise around these specimens. Habits form—some good, some suboptimal, and some dangerous. The key to a safe laboratory is introspection and continuous process improvement. Dangerous habits should be identified and corrected. When accidents do occur, they can and should be used as learning experiences. Indeed, the concepts outlined in this chapter are the result of years of listening to how colleagues have cut themselves and a determination not to make the same mistakes. While this chapter focuses on sharps safety since it has the most direct impact on the quality of the grossing technique, the handling of other safety-related issues, such as radiation, airborne and splashed infectious exposures, and toxic chemicals, can be treated in a similar fashion.

While listening to and remembering stories about sharps injuries over the years has been an invaluable source of wisdom about how to handle sharps safely, the goal of this chapter is to inspire a culture of safety that bypasses some of the need to learn from others' misfortunes. Sharps injuries occur in somewhat predictable patterns, and I have used those to formulate personal practices that have successfully prevented sharps injuries in my career. Prosecting will always be dangerous, and no system could ever guarantee total safety in the grossing room. The simple suggestions presented below are a reasonable starting point that prosectors may use and refine according to local practices and experience.

Sharps practices to avoid

Absolute statements are difficult because exceptions invariably exist. Indeed, there are some well-respected procedures for certain specimens that encourage one or more of the practices listed as undesirable below. Proponents of dangerous techniques argue that injuries will only occur if the prosector is not paying adequate attention. There is certainly truth to this statement, but similar sophistry could be used to reintroduce mouth-pipetting in the blood bank. As long as humans do this work, there will be muscle spasms, slips, and absent-minded moments. The safety-oriented systems-based laboratory cannot eliminate human factors, but it can discourage or forbid inherently unsafe practices. With some imagination and thought, safe alternatives to risky practices can always be found. The key to safety is introspection.

- **Never point the blade or tip towards oneself or another person.** Several grossing scenarios appear to lend themselves to holding a specimen and cutting so that the blade stops just shy of the prosector's hand. For example, some prosectors have been known to hold lumpectomy specimens during slicing for extra

support so that thin slices can be achieved. Doing this is exceedingly dangerous. Cutting boards are at the grossing station for a practical reason: to avoid prosectors from cutting into their hands. They should be used that way. Extra support can be achieved with broad spatulas or implements that meet the board at a right angle. The end goal should be to keep the specimen steady and hands far away from sharps. Whenever faced with the temptation to cut this way, I have trained myself to step back and think of an alternative. Doing so may take more time to begin, but the gains in productivity that come later from always being safe at the grossing station far outweigh an initial outlay of effort and imagination.

- **Never touch the sharp edge or tip against any part of the body.** For dissection along a vessel or other tubular structure, some dissection practitioners encourage the prosector to place a finger in the structure and then cut through the wall until the sharp tip touches the finger. The problem with this practice is that a sharp tip can snag the glove and cause formalin or bloodborne pathogen exposure at best, or a cut on the finger at worst. Better practices would be to use scissors, a blunt probe, or a butt-end of a unbladed scalpel to absorb the tip of the blade.
- **Never keep hidden sharps at the grossing table.** It is important to know where sharp objects are at all times. If a sharp object is not in hand, then it should be stored in a visible location a safe distance away from the work area. Needles and blades that are hidden can make a most unwelcome appearance when least expected.
- **Never use dull blades.** A blade should cut through tissue easily with the application of minimal force. Because dull blades require more force, there is more potential for accidents if the specimen slips. A well-stocked grossing station should contain abundant, readily accessible replacement blades so that there should never be an excuse to make do with a dull blade.

Sharps practices to encourage

While categorically discouraged practices are easy to spot, it is useful to have good practices to replace bad ones. Some of these may seem pedestrian, but in the rush of a busy gross room, it is easy to fall into bad habits especially for prosectors who have had little exposure to sharps and for those who have had a lot of exposure and have dangerous practices engrained. Therefore, some introspection is needed to strive for the best practices, for grossing is inherently part art and part science.

- **Choose the right blade for the cut.** An ideal cut is a single smooth stroke of the blade through the tissue. If a 30-cm sarcoma needs to be breadloafed, then a long sectioning knife is preferable to a 2-cm scalpel; using a small scalpel for this job mottles the cut edge, prevents a straight cut, and increases the mileage on the small blade such that the blade will dull quickly, and dull blades present a risk for slippage and injury. If a 2-cm lipoma needs to be sectioned, then a straight razor or a scalpel is preferable to a 20-cm sectioning knife, for an excessively long knife is difficult to control on a small piece of tissue. Scissors are an excellent choice. While examples such as these are straightforward, the pitfalls begin when one instrument is more accessible than another and compromises are made. Therefore, before making a cut, a good first step is to think about the cut and match the right blade to the task. A well-stocked, well-arranged grossing station lessens the temptation to use blades inappropriately. Prosectors protect themselves by ensuring their grossing station is well stocked and well arranged before the cutting begins.
- **Before picking up a sharp object with one hand, think about how the other hand will be protected.** The hand without the sharp object is at risk for getting injured whether from a careless motion, slippage of the specimen, or any number of events that can bring that hand into contact with the blade. Therefore, it is a good idea to think about protecting the hand without the sharp object before a sharp object is even held. Forceps, bear claws, clamps, and probes should be available at the grossing station at all times. Making a habit of reaching for one of these with the nondominant hand before the dominant hand picks up the blade is excellent protection against injury.

  Metal-wire reinforced-knit "cutting gloves" are popular among some prosectors as a protection against cutting the "dumb hand." Certainly they are better than no protection if bad cutting practices are being used that place the prosector at risk. However, one must consider the disadvantages of cutting gloves. Obviously

they create a false sense of security since they are not sharps-proof. Furthermore, cutting gloves are uncomfortable, bulky, and tight; they can lead to less than ergonomic ways of holding dissecting instruments, which in turn can lead to less than optimal cuts. Additionally, cutting gloves are soiled easily and too expensive to be replaced with every glove change, so cutting gloves come with an extra distraction of protecting the protection. Thus, while the decision to use cutting gloves is a matter of personal preference, there is a case to be made against cutting gloves, and using this safety equipment should only be done with the realization that there is no substitute for safe practice.

- **Beware of blade changes.** Cryotomes, scalpels, bone saws, and long sectioning handles all have specialized, preferably disposable blades that need to be changed frequently. Changing a blade is a safety measure since cutting with a sharp blade is safer than cutting with a dull one as described above. However, changing blades can be dangerous if done improperly, so it behooves the laboratory and the prosector to have the right procedures and equipment readily available for each type of blade change. One of the most common situations I have seen for colleagues cutting themselves is with blade changes. Keeping a few blade changing guidelines can go a long way in preventing these injuries. As described above, protecting the dumb hand is important during cutting, and protecting the dumb hand during blade changes is just as important. In cryostats, it is useful to push the blade off of the stage; the butt-end of a brush is ideally suited to this task. If the blade cannot be safely picked up from the noncutting side, then a pair of hemostats or forceps can be used. Replacing the blade in a cryostat sometimes requires a little downward pressure to make sure the blade is straight before it is clamped into the stage; a finger should never be used for this purpose. A brush end works well for this purpose too. Scalpel blades are even more dangerous because even the noncutting surfaces can be angular and sharp. The use of clamps to handle these blades is often prudent.
- **Cut dry specimens.** Wet specimens are at risk of slipping during the cut. Therefore, it is necessary to keep the workspace and specimen as dry as possible. Dry the cutting board after cleaning it. Fresh specimens are often bloody and should be dabbed with a clean absorbent paper towel before cutting; dabbing should continue with new paper towels until the paper towel comes off clean or with very minimal blood. This is impractical for specimens such as placentas, so placing these on extra-absorbent pads is often the best bet. If ink is going to be applied, then it should be added in a focused, concentrated manner, dabbing off excess with clean absorbent paper towels. Ink should never be dumped. Not only is ink dumping wasteful, it increases the risk of ink going into places that are not margins. From a safety perspective, ink dumping is unsafe because it makes the specimen wet, and wet specimens are a slippage risk. Ink dumping also makes a mess that can hide where instruments are, increasing the chance of being unpleasantly surprised. If an ink fixative is being used, such as Bouin's or acetone, the ink should be patted dry before the addition of this material. One way to tell if the ink is dry is if it loses its wet sheen and appears dull. Ink should not be dumped. It should be dabbed gently with an absorbent paper towel. This may take some time, but if the margin is worth inking, then it is worth the time to get right.
- **Stabilize the specimen.** Most specimens have surfaces that sit better than others. Sometimes those surfaces are an excellent choice for stabilizing the specimen. For example, cutting through a wide resection of a skin ellipse works much better when the skin ellipse is lying skin down so that it does not roll or slide on the fat and so that the final cut at the board end is through the tough skin, which is immobilized under the weight of the rest of the specimen as well as the forceps or spatulas used to hold the specimen in place. However, other specimens lie in ways that are poor choices for cutting. For example, a lung sits best on its hilum, but cutting the lung from the periphery down to the hilum can lead to poor visualization of the tumor with respect to important hilar structures. For this reason, it is ideal to use long probes into the hilar structures and through the parenchyma and pleura so that the lung can sit on the hilum, and the long probes form a convenient guide to stabilize the lung and guarantee that the knife will cut the hilar structures in half.
- **Cut downwards towards the cutting board.** One of the most common dangerous techniques being taught to prosectors is the cut in which the blade is parallel to the cutting board and the prosector's hand provides

the support. There are several problems with this cut. First, it usually provides a less-than-smooth cut surface because it is often difficult to get a clean sweep based on the stabilization of friction between the specimen, hand, and cutting board. Second, the dumb hand holding the specimen is unprotected; a stray finger, thenar eminence, or apron sleeve can get snagged on the blade and lead to injury or exposure. Finally, cuts of this style are done with the blade leaving the specimen into open air. If the space next to that specimen is not clear, mess or injury of an adjacent object or person can occur. All these problems are obviated if the cut goes towards the cutting board. The specimen can be stabilized far better with long probes and spatulas, gravity helps the cut, and prosectors are much more in control of the blade when they think about cutting the specimen without worrying about slipping and cutting their hands.

- **Think before the cut.** With the correct blade chosen, the dumb hand protected, a sharp blade ready, and the specimen stabilized, it is sometimes helpful for the prosector to pause and consider the cut. Thinking through the cut forces the prosector to double-check all these things to make sure they are right before the cut rather than during it. Thinking through the cut also forces the prosector to consider what tools may be required next and to have those ready. For example, if a 5-kg cystic structure is about to be sliced, it may behoove the prosector to ensure proper drainage and absorbent materials. Diving into a dissection without clearly considering the objectives can lead to mess, waste, suboptimal sections, unsafe practices, and even substandard grossing, which may have an effect on patient care. In subsequent chapters, specific objectives are presented. These give concrete objectives that the prosector should be considering before making cuts. From a safety perspective, however, stopping before a cut and introspecting if the posture is safe, if the blade is sharp, if the prosector is protected, if the specimen is secure, and if the cut about to be executed is optimal is good practice. It may seem trite at first, but if applied unflinchingly, this practice can save a lot of pain downstream. Eventually this practice becomes second nature and almost subconscious.
- **Decide the fate of the sharp while it is being held.** A sharp object is a liability. Once its purpose is complete, it needs to be safely disposed of in an appropriately sized sharps container. Disposing of sharps is hazardous when the containers are too full for easy disposal or when the blades stick on their handle. The same principles outlined for changing sharps apply to disposing of them: attempts should be made for hands never to touch the sharp object. For example, long blades should slide easily into the disposal container and be released off of the handle, and scalpel blades can be placed into the disposal on the end of a clamp.

Conclusion

As the following chapters will show, gross specimen prosection is increasingly dictated by the needs of standardized tumor staging guidelines. At the same time, trends in modern pathology practice increasingly relegate prosection to pathology assistants and trainees. As such, the role of the attending pathologist in this critical step of the diagnostic process is evolving into that of a high-level supervisor. With ultimate responsibility for the final diagnosis and a vested interest in the well-being of all laboratory personnel, the pathologist needs to assume the role of creating a safety culture, and the grossing room is a prime example of an area that needs strong initiatives in this regard. The practical guidelines above are based on real-world experience with injuries in the grossing room as well as substandard grossing results that could have been remedied with some focus on the ideal cut: a cut that is clean, smooth, and in harmony with personal safety.

1. Ductal Carcinoma In Situ

Qingqing Ding, MD, PhD; Fang Fan, MD, PhD

Lumpectomy (also called *partial or segmental mastectomy*) is a breast-conserving surgery defined as complete surgical resection of a primary tumor as well as some surrounding normal breast tissue, with a goal of achieving negative margins. Lumpectomy may be performed with image guidance, which includes wire-guided localization and radioactive (or magnetic) seed localization.

Total mastectomy or simple mastectomy is defined as complete removal of all breast tissue, which may be performed in conjunction with a sentinel node biopsy. Two types of total mastectomy—the skin-sparing mastectomy and the nipple-sparing mastectomy—are usually performed for patients with ductal carcinoma in situ (DCIS) who wish to undergo immediate breast reconstruction.

Accurate pathologic reporting of DCIS is essential to guide postsurgical treatment, such as radiation therapy, and provide information to predict prognosis. Adequate tumor sampling and thorough examination of essential margins are of utmost importance in processing surgical specimens with DCIS. Careful review of radiologic imaging (mammography, ultrasound, and magnetic resonance imaging [MRI]), clinical history, and preoperative biopsy is necessary before grossing any breast resection specimen.

I. Indications for lumpectomy or mastectomy for DCIS

Lumpectomy

- Lesion should be limited to one quadrant or section of the breast.
- Cosmetically acceptable resection is achievable given the extent of disease relative to the size of the breast.
- Histologically negative margins are obtainable with lumpectomy.

Mastectomy

- DCIS lesion does not meet the above criteria, usually due to large size (>5 cm) or multicentric disease.

II. What do we expect to see in the lumpectomy and mastectomy specimens macroscopically and microscopically?

Based on the degree of nuclear atypia, DCIS is classified into low, intermediate, and high grade. It can show multiple growth patterns, such as solid, cribriform, papillary, and micropapillary patterns. Microcalcifications are usually seen in association with DCIS. High-grade DCIS can form a mass-like lesion, but low-grade DCIS usually does not.

In cases of biopsy-confirmed DCIS, comprehensive evaluation of the involved breast tissue is critical to rule out possible microinvasion or focal invasive carcinoma, especially for those with high nuclear grade. Another important element in pathologic reporting of DCIS is the status of margins. According to the current consensus guideline by the Society of Surgical Oncology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology, a margin greater than 2 mm is considered as the standard for an adequate margin for DCIS.[1]

III. Photo documentation of lumpectomy and total mastectomy specimens

Once received, the lumpectomy specimen should be radiographed immediately to confirm the presence/number of the biopsy clip and/or seed in order to ensure removal of the targeted lesion. It is not necessary to radiograph a total mastectomy specimen immediately, but taking one image to localize the biopsy clip and calcification is encouraged. Then, the specimen should be grossly examined to correlate the size and location of lesional tissue with preoperative radiologic imaging. The total mastectomy specimen should also be examined for any skin and/or nipple change.

IV. Dissection technique: step-by-step description

1. Orient and ink specimen.

The orientation of lumpectomy or total mastectomy specimen is usually designated by the surgeon (such as long stitch-lateral and short stitch-superior, as shown in Figures 1-1A and 1-2A). If there is any question about the orientation, the surgeon should be contacted immediately. The specimen is measured in three dimensions, including the attached skin on total mastectomy specimen, and inked. Inking should be careful as the ink may penetrate deep into tissue cleft and cause a false-positive margin. Different hospitals may have different ink codes. Generally, five or six colors are used for the lumpectomy specimen, whereas three colors are adequate for the total mastectomy specimen. See the following ink code examples.

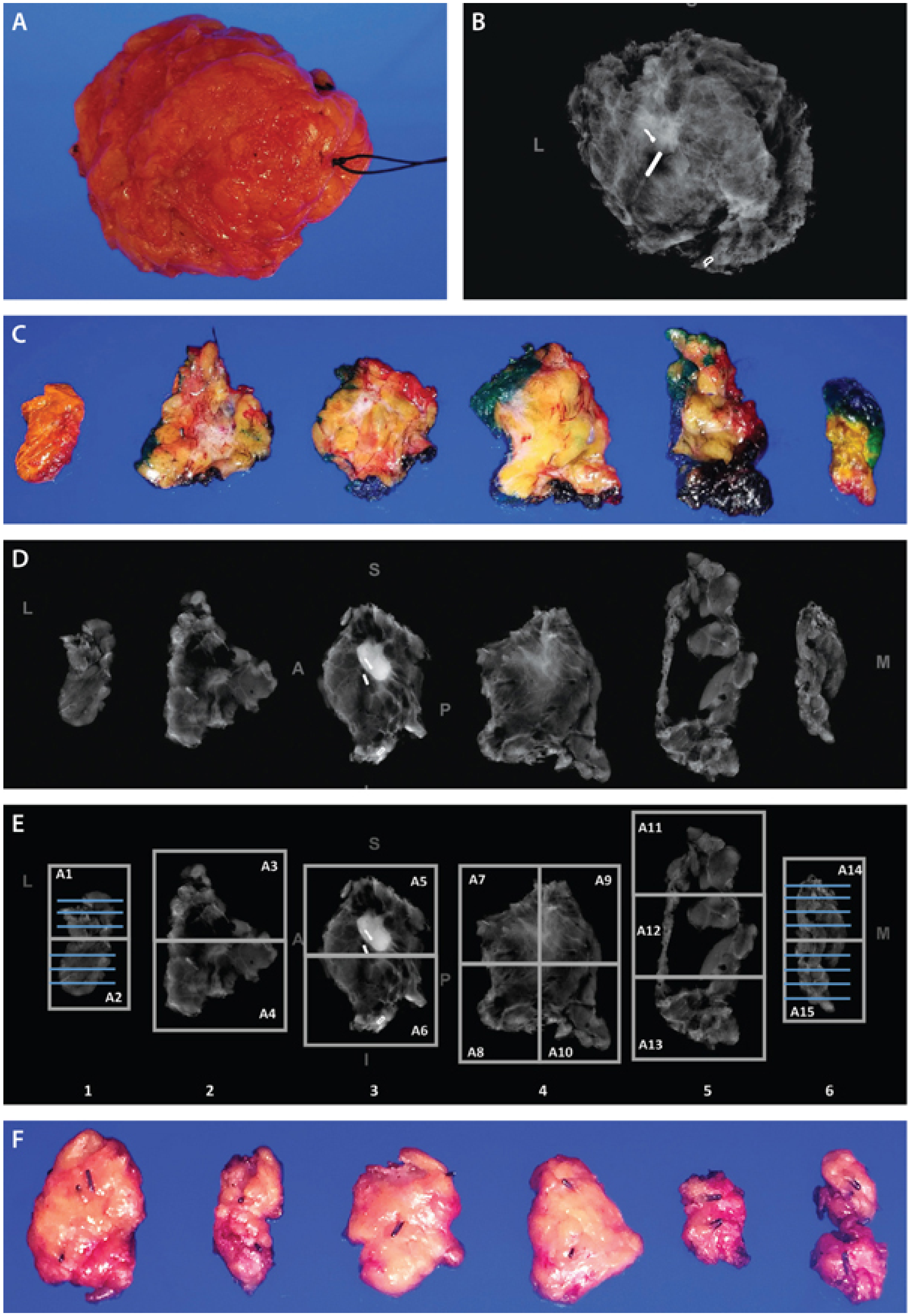

Figure 1-1. Lumpectomy gross specimen. A. A typical lumpectomy gross specimen with short and long stitches designating orientation. B. X-ray film of the lumpectomy specimen to show biopsy clips and radioactive seed. C. Serial sections of the lumpectomy specimen along the lateral-medial axis, with six colors to indicate different margins. D. X-ray film of the serial sections of the lumpectomy specimen to show tumor nodule with associated biopsy clip and radioactive seed. E. Sampling of the lumpectomy specimen. F. Six additional shave margins for the lumpectomy.

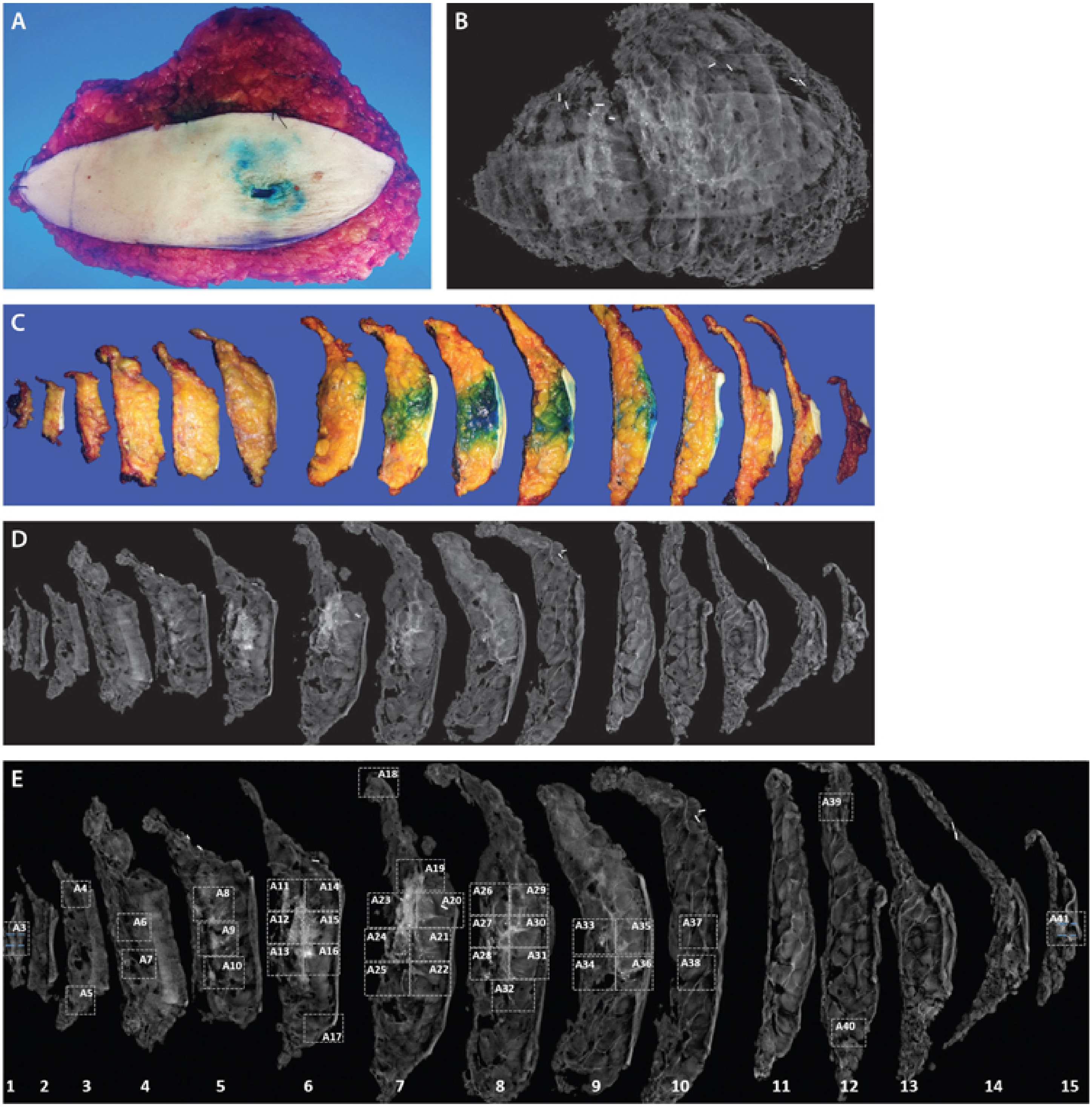

Figure 1-2. Total mastectomy gross specimen. A. A typical total mastectomy gross specimen with short and long stitches designating orientation. B. X-ray film of the mastectomy specimen to show the area of microcalcification with biopsy clips. C. Serial sections of the mastectomy specimen along the lateral-medial axis. D. X-ray film of the serial sections of the mastectomy specimen to show the microcalcification area with biopsy clips. E. Sampling of the mastectomy specimen.

Ink code for lumpectomy

Superior: blue

Inferior: green

Anterior: yellow

Posterior: black

Medial and lateral: orange

Ink code for total mastectomy
Superior/anterior: blue
Inferior/anterior: orange
Posterior: black
Nipple areola complex (for nipple-sparing mastectomy, Figure 1-3): yellow

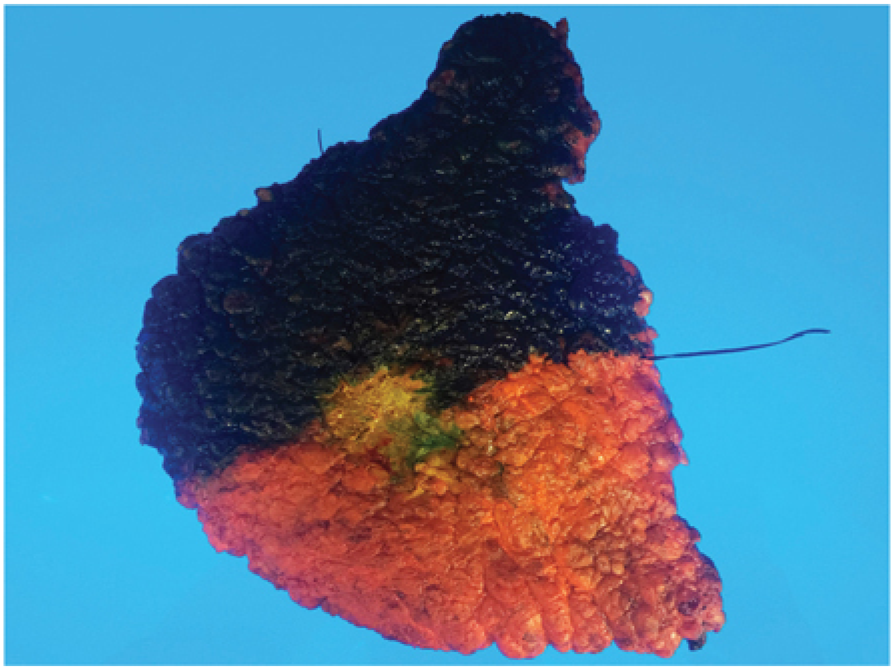

Figure 1-3. A typical nipple-sparing mastectomy gross specimen, with different inks to show superior/anterior (blue) aspect, inferior/anterior (orange) aspect, and nipple areola complex (yellow).

2. Serially section the specimen.

After inking, the specimen is serially sectioned along the lateral-medial axis (from lateral to medial for left breast and from medial to lateral for right breast). If the lumpectomy specimen is wire guided, the wire should be carefully removed before slicing the specimen. The specimen should be sectioned at the same intervals (approximately 0.5-1.0 cm) throughout, which will be helpful to evaluate the tumor size after microscopic examination. For the lumpectomy specimen, except the lateral and medial tips, each slice should have four color-inked margins (Figure 1-1C). For the total mastectomy specimen, we suggest that the specimen be placed on the gross table with anterior surface down and then cut from the posterior surface to make sure every slice contains posterior margin. After sectioning, all the slices are placed on a plastic plate in order (from lateral to medial if left breast, from medial to lateral if right breast; Figures 1-1C and 1-2C). Then each slice is carefully examined to determine the size and location of lesion, number of involved slices, and distance of lesion to different margins. If there are multiple lesions, the location of each lesion and the distance between them should be documented. In addition, the specimen should be palpated to detect any possible intramammary lymph node.

With the wide usage of radioactive (or magnetic) seed localization in lumpectomy surgery, specimen radiographing is usually required to document the presence/number of the seeds and biopsy clips (Figure 1-1D). If a radioactive seed is located, it should be carefully removed and placed in a designated container per institutional radioactive safety regulations. If adequate margin status is questioned, radiographing the sliced lumpectomy specimen will contribute greatly in the determination of margin distance and delineation of lesional tissue/microcalcification in the specimen.

For a total mastectomy specimen, when multiple lesions/areas of suspicious calcifications are present or when the lesion is ill defined, an x-ray film of the sliced specimen can be used to determine the size and distribution of microcalcifications, which helps to sample the specimen accurately in correlation with the gross examination.[2] Moreover, if the lesion is close to the margin but the specific distance is difficult to evaluate

grossly, an x-ray film of the sliced specimen will make the intraoperative margin evaluation more accurate. For example, in Figure 1-2D, the microcalcifications approach anterior/superior and deep margins focally, which is difficult to appreciate grossly.

After successful examination of the specimen, the surgeon should be informed intraoperatively about the presence and number of biopsy clips and/or radioactive seed, as well as the distance between the lesion and margins. If the lesion or microcalcifications approach a certain margin, re-excision of that margin is recommended intraoperatively to avoid a potential subsequent second surgery for re-excision.

3. Properly and adequately sample specimen.

If the lesion has been previously biopsied, the area with biopsy clip is the targeted area for sampling. Other suspicious areas (microcalcifications) without previous biopsy also need to be sampled.

For small lumpectomy specimens, the entire specimen with all six margins is submitted. For the two end margins, perpendicular sections of the margins should be submitted (Figure 1-1E).

For larger lumpectomy specimens, adequate representative sections of the tumor with adjacent margin should be submitted. If submitting representative sections, the cross-section of the tumor or microcalcification in each involved slice with closest margins must be submitted, followed by adjacent normal-appearing breast tissue in adjacent slices, as well as the two end margins.

For lumpectomy, additional shave margins may be taken and designated by the surgeon (Figure 1-1F). Ink the true margin in black and the opposite side with another color, such as blue; then serially section the entire margin (perpendicularly to show black-inked true margin) and submit all sequentially.

For mastectomy, if there is a large tumor or large area of microcalcification, adequate representative sections should be submitted to search for possible microinvasion or small foci of invasive carcinoma, especially in cases of DCIS with high nuclear grade (Figure 1-2E). First, the cross-section of the tumor or microcalcification area in each involved slice with closest margins are submitted. Next, adjacent normal-appearing breast tissue in the adjacent slices is submitted. If there are multiple tumors or areas of microcalcification, the tissue between the adjacent two lesions should be submitted in order to document if the two lesions represent a single contiguous lesion or two separate lesions. In addition, entire nipple, nipple base, and representative skin section should be submitted. For the nipple-sparing mastectomy, the nipple areola complex will be submitted. If the tumor is close to the nipple, frozen diagnosis may be already performed on nipple areola complex. For the quadrant that is not involved by tumor/microcalcification, representative sections of each quadrant should be submitted. Finally, the representative lateral and medial slices, as well as any grossly identified intramammary lymph node, are also submitted.

The clearly documented gross description must include radiographic findings, ink code, and section code.

V. Sample gross description

Lumpectomy

Right breast, radioactive seed–localized lumpectomy: A lumpectomy specimen labeled “short stitch superior and long stitch lateral” measures 4.0 cm (from medial to lateral) x 3.5 cm (from superior to inferior) x 2.6 cm (from anterior to posterior). Radiography of the specimen reveals two biopsy clips and a radioactive seed. After inking, the specimen is serially sectioned from medial to lateral into six slices, with biopsy clips and radioactive seed in slice #3. The biopsy clips and radioactive seed are removed, and the radioactive seed is put in the specific container.

There is an ill-defined fibrotic nodule in slice #3, measuring 1.1 x 0.8 x 0.5 cm, which is 0.5 cm to the anterior, 0.9 cm to the posterior, 0.6 cm to the superior, 1.5 cm to the inferior, 1.5 cm to the lateral, and 2.1 cm to the medial margins. No other mass lesion or suspicious microcalcification is identified in other slices.

Ink code

Superior: blue

Inferior: green

Anterior: yellow

Posterior: black

Medial and lateral: orange

Section code (Figure 1-1E)

A1-2: Lateral margin, perpendicular sections of slice #1

A3: Superior 1/2 of slice #2

A4: Inferior 1/2 of slice #2

A5: Tumor with superior 1/2 of slice #3 (with biopsy clip)

A6: Inferior 1/2 of slice #3

A7: Anterior/superior 1/4 of slice #4

A8: Anterior/inferior 1/4 of slice #4

A9: Posterior/superior 1/4 of slice #4

A10: Posterior/inferior 1/4 of slice #4

A11: Superior 1/3 of slice #5

A12: Middle 1/3 of slice #5

A13: Inferior 1/3 of slice #5

A14-15: Medial margin, perpendicular sections of slice #6

Lumpectomy with additional shave margins

B. Right breast, additional superior margin, excision: An additional superior margin specimen measures 3.2 x 2.7 x 0.7 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in B1-B3.

C. Right breast, additional inferior margin, excision: An additional inferior margin specimen measures 2.8 x 1.7 x 0.6 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in C1-C2.

D. Right breast, additional lateral margin, excision: An additional lateral margin specimen measures 3.7 x 2.6 x 0.8 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in D1-D3.

E. Right breast, additional medial margin, excision: An additional medial margin specimen measures 3.6 x 2.6 x 1.0 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in E1-E3.

F. Right breast, additional posterior margin, excision: An additional posterior margin specimen measures 2.2 x 1.4 x 0.5 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in F1-F3.

G. Right breast, additional anterior margin, excision: An additional anterior margin specimen measures 3.4 x 1.6 x 0.8 cm, with clips designating true margin. The true margin is inked black, the opposite side is inked blue. The specimen is serially sectioned perpendicularly and submitted entirely in G1-G3.

Total mastectomy

Right breast, total mastectomy: A total mastectomy specimen labeled “short stitch superior and long stitch lateral” measures 18.6 cm (from lateral to medial) x 17.4 cm (from superior to inferior) x 3.8 cm (from anterior to posterior), with attached 18.1 x 8.3 cm elliptical tan-white skin and 1.2 x 1.1 x 0.6 cm everted nipple. Radiography of the specimen reveals two biopsy clips in an area with approximately 6 x 5 cm microcalcifications. After inking, the specimen is serially sectioned from medial to lateral into 15 slices, with biopsy clips in slice #7 and nipple in slice #10 and #11.

There is an ill-defined, firm nodule in slices #5 to #9, measuring approximately 6.0 x 5.0 x 2.5 cm. The nodule is located in the upper outer quadrant 10-11 o’clock, with 1.8 cm to the nipple, 1.2 cm to the closest superior skin margin, 4.2 cm to the closest inferior skin margin, 0.2 cm to the anterior/superior, 0.6 cm to the posterior, 5.2 cm to the superior, 6.3 cm to the inferior, 4.8 cm to the lateral, and 7.2 cm to the medial margins. Radiography of the specimen shows two biopsy clips in slice #7 and extensive microcalcifications associated with nodule in slices #5 to #11. The microcalcifications approach the anterior/superior and posterior margins and extend to the dermis and nipple base. No other mass lesion or suspicious microcalcification is identified in

other slices. No skin lesion or induration/reaction is identified. The remaining breast tissue is composed of 30% fibrotic tissue and 70% adipose tissue.

Ink code

Anterior/superior: blue

Anterior/inferior: orange

Posterior: black

Section code (Figure 1-2E)

A1: Entire nipple, serially sectioned (for nipple-sparing mastectomy, submit the nipple areola complex)

A2: Nipple base

A3: Representative lateral edge, perpendicular sections of slice #1

A4: Representative section of upper outer quadrant in slice #3

A5: Representative section of lower outer quadrant in slice #3

A6-7: Adjacent tissue to tumor in slice #4

A8-10: Tumor in slice #5 (from superior to inferior)

A11-13: Posterior portion of tumor with posterior margins in slice #6 (from superior to inferior)

A14-16: Anterior portion of tumor in slice #6 (from superior to inferior)

A17: Representative inferior/anterior margin with skin in slice #6

A18: Representative superior margin in slice #7

A19: Tumor with closest anterior/superior margin in slice #7

A20: Tumor with closest superior skin margin in slice #7

A21-22: Anterior portion of tumor in slice #7 (from superior to inferior)

A23-25: Posterior portion of tumor with posterior margins in slice #7 (from superior to inferior, with two clips in A23)

A26-28: Posterior portion of tumor with posterior margins in slice #8 (from superior to inferior)

A29-31: Anterior portion of tumor in slice #8 (from superior to inferior)

A32: Tissue with microcalcifications below A28 and A31 in slice #8

A33-34: Posterior portion of tumor with posterior margins in slice #9 (from superior to inferior)

A35-36: Anterior portion of tumor with skin in slice #9 (from superior to inferior)

A37-38: Adjacent tissue to tumor in slice #10

A39: Representative section of upper inner quadrant in slice #12

A40: Representative section of lower inner quadrant in slice #12

A41: Representative medial edge, perpendicular sections of slice #15

VI. Common pathologic findings in lumpectomy and mastectomy for DCIS

- DCIS, low nuclear grade, solid pattern (Figure 1-4A)
- DCIS, high nuclear grade, solid pattern with comedonecrosis (Figure 1-4B)
- DCIS with microinvasion (Figure 1-4C)
- DCIS with invasive carcinoma (Figure 1-4D)

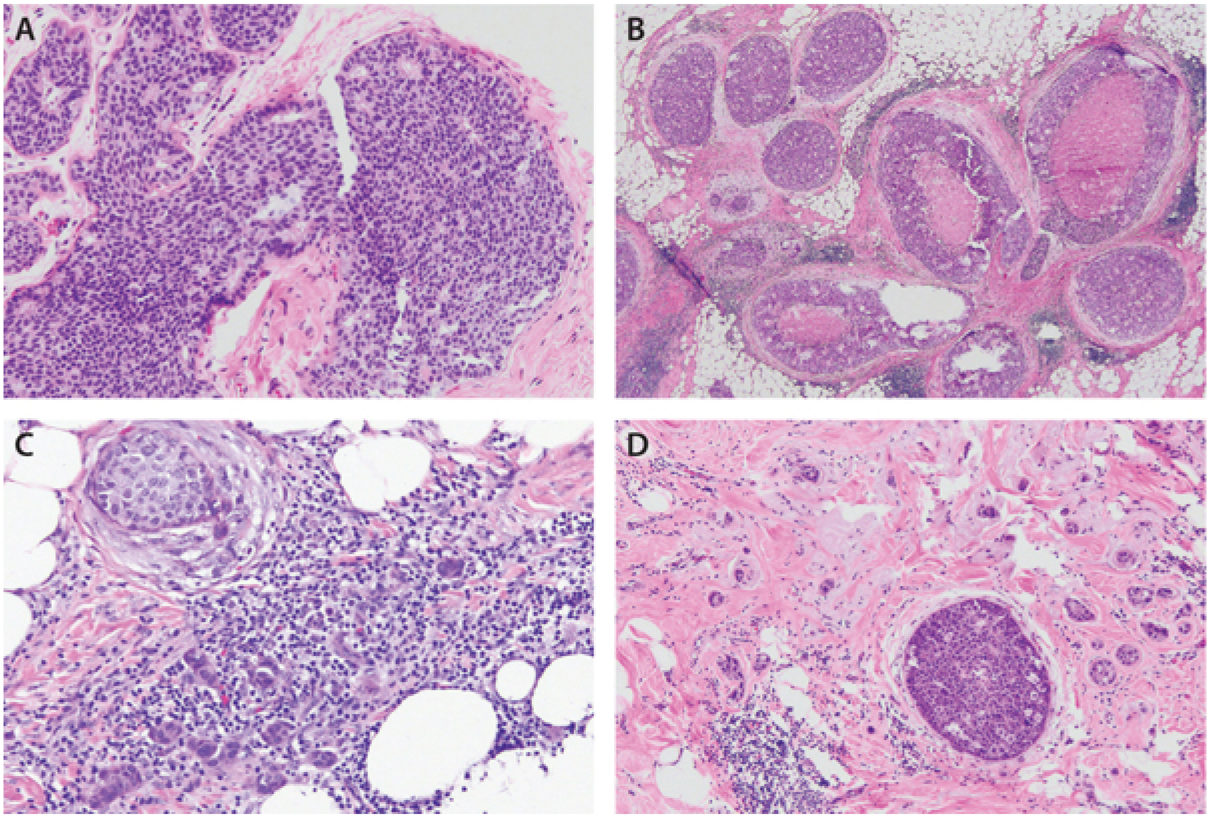

Figure 1-4. Microscopic image of ductal carcinoma in situ. A. Low nuclear grade, solid pattern without necrosis. B. High nuclear grade, solid pattern with comedonecrosis. C. With microinvasion (<1 mm). D. With focal invasive carcinoma (1.5 mm).

VII. Common potential staging pitfalls and solutions

Missing the microinvasive carcinoma (≤1 mm) or small focus of invasive carcinoma (>1 mm but ≤5 mm) is the most common pitfall in staging. For every high-grade DCIS, it is important to think about the potential microinvasion or even invasive carcinoma. It is critical and required to review all the clinical information, such as clinical examination and radiologic results, before grossing the specimen. Knowing all the information about the current DCIS lesion—such as tumor size, location, microcalcification area and extent—is necessary for accurate sampling. For small tumors, the entire lesion should be submitted. If the tumor is large and submission of the entire tumor is not practical, adequate representative sections from each slice with tumor/microcalcifications are still required. In addition, areas with suspicious microcalcifications should not be missed. If the tumor is not easy to identify grossly, radiography of the specimen slices will help to detect the area with microcalcifications.

Occasionally, isolated tumor cells (ITCs) can be identified in the axillary sentinel lymph nodes, especially in DCIS with papillary and/or micropapillary growth patterns, which may be due to drainage of detached tumor cells to the axillary lymph node after previous biopsy. However, it also may indicate the potential presence of true invasive carcinoma associated with DCIS. Therefore, when ITCs are identified, careful reviewing of the record of grossing procedure and re-reviewing of the slides microscopically is required to determine if additional tissue sampling is needed. If micrometastasis is identified without microinvasive or invasive carcinoma identified in the breast specimen, submission of all remaining tumor is recommended if the entire tumor has not been submitted previously.

VIII. What should be included in the pathology report?

- Description of specimen and procedure
- Description of the type of tumor (DCIS), nuclear grade, architectural pattern, presence or absence of necrosis and associated microcalcifications

Per the current College of American Pathologists (CAP) cancer protocol for DCIS, additional information needs to be supplied, as listed below[3]:

- Description of the DCIS site and position
- Tumor size and extent
- Status of margins (positive or negative, the closest margin)
- For positive or close margins (<2 mm), specify extent (focal, minimal/moderate, or extensive) of the DCIS near the positive/close margin
- Status of regional lymph nodes
- pTNM stage

If there is microinvasive carcinoma or invasive carcinoma, it is necessary to give the invasive tumor type and Nottingham histologic score, as well as detailed information, by following the CAP protocol for invasive carcinoma (see chapter 2, *Invasive Breast Carcinoma*).

Sample final diagnosis

Right breast, total mastectomy:

Ductal carcinoma in situ (DCIS), high nuclear grade, solid and cribriform patterns with comedonecrosis and associated microcalcifications

See tumor checklist.

DCIS checklist:

- Procedure: Total mastectomy
- Specimen Laterality: Right
- Tumor Site: Upper outer quadrant
- Position: 10-11 o'clock
- Size (Extent) of DCIS
  - Estimated size (extent) of DCIS: approximately 6.0 cm
  - Additional dimensions: 5.0 x 2.5 cm
- Histologic Type: Ductal carcinoma in situ
- Architectural Patterns: Solid and cribriform
- Nuclear Grade: Grade III (high)
- Necrosis: Present, central (expansive "comedo" necrosis)
- Microcalcifications: Present in DCIS
- Margins
  - Uninvolved by DCIS
    - Distance from closest margin (millimeters): 2.1 mm
    - Specify closest margin: Anterior/Superior
- Regional Lymph Nodes: 3 axillary sentinel nodes, negative for carcinoma
- Pathologic Stage Classification: pTis (sn)N0 Mn/a
- Primary Tumor (pT)
  - pTis (DCIS): Ductal carcinoma in situ.
- Regional Lymph Nodes (pN)
  - (sn): Sentinel node(s) evaluated.
  - pN0: No regional lymph node metastasis identified or ITCs only
- Distant Metastasis (pM)
  - Not applicable

References

1. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. *J Clin Oncol.* 2016;34(33):4040-4046.

2. Huo L. From the gross room: a practical approach to grossing breast specimens. *Ann Diagn Pathol.* 2011; (15):291-301.
3. Fitzgibbons PL, Connolly JL, Bose S, et al. Protocol for the Examination of Resection Specimens From Patients With Ductal Carcinoma In Situ (DCIS) of the Breast. 2020. Available at www.cap.org/cancerprotocols. Accessed August 25, 2020.

2. Invasive Breast Carcinoma

Fang Fan, MD, PhD; Qingqing Ding, MD, PhD

Breast resection specimens for invasive breast carcinoma include lumpectomy and mastectomy. *Lumpectomy* (also called *breast-conserving therapy*) implies removal of the tumor with a rim of normal tissue without removing the whole breast. *Mastectomy* implies removal of the entire breast. Depending on the extent of the surgery, mastectomy includes simple (total) mastectomy, nipple-sparing mastectomy, skin-sparing mastectomy, and modified radical mastectomy. The definitions of these procedures are listed below.

I. Indications for lumpectomy and mastectomy

If the breast cancer (either single focus or multiple foci) can be removed with adequate circumferential clear margins without major cosmetic damage, a lumpectomy is indicated. The nipple is usually not included in the lumpectomy specimens. A lumpectomy specimen may also be designated as partial mastectomy or quadrantectomy. Breast-conserving surgery with radiation therapy provides the same level of overall survival as mastectomy for the patient.[1]

Absolute contraindications for lumpectomy include[2]:

- Multicentric disease
- Locally advanced disease
- Diffuse (malignant) microcalcifications
- First or second trimester of pregnancy
- Mutations of *BRCA1* and *BRCA2* genes
- History of radiation to the chest wall

If the breast cancer is large or involves multiple quadrants, then a mastectomy is indicated. The following is a list of various mastectomy procedures:

- Simple (total) mastectomy: removal of all breast tissue with the overlying skin, including the nipple and areola
- Skin-sparing mastectomy: removal of all breast tissue with the nipple and a narrow rim of skin
- Nipple-sparing mastectomy: removal of all breast tissue without the overlying skin and nipple
- Modified radical mastectomy: total mastectomy plus an axillary lymph node dissection
- Radical mastectomy: total mastectomy plus axillary lymph node dissection and removal of the pectoralis major and pectoralis minor muscles

II. What do we expect to see in the lumpectomy and mastectomy specimens macroscopically and microscopically?

Many patients are treated with neoadjuvant therapy, such as targeted or systemic chemotherapy, before surgery. The gross and microscopic appearances of these specimens are different from those without neoadjuvant therapy.

Specimens without neoadjuvant therapy

In both the lumpectomy and mastectomy specimens, we expect to see invasive breast carcinomas. Accurate measurement of tumor size, incorporating both macroscopic and microscopic measurements, is critical for the T staging of the tumor. It is also important to correlate the gross and microscopic findings with the corresponding imaging findings to ensure that all suspicious imaging findings are sampled appropriately.

Margin assessment is also critical in evaluating lumpectomy and mastectomy specimens. In lumpectomy specimens, the distance of invasive carcinoma to all six margins should be measured grossly and microscopically. In mastectomy specimens, the distance of invasive carcinoma to the closest margins should be measured grossly and microscopically.

Specimens with neoadjuvant therapy

In both the lumpectomy and mastectomy specimens from patients who have received neoadjuvant therapy, it is very important to identify the tumor bed grossly.[3] The tumor bed appears as an irregular area of rubbery fibrous tissue. In cases with substantial treatment response, identifying the tumor bed can be challenging. Use of radiologic information and locating previous biopsy clip are essential in identifying the tumor bed. Measurement of tumor bed size and the distance of the tumor bed to all margins are required in gross and microscopic evaluations.[3]

III. Typical gross photos of lumpectomy and mastectomy for invasive breast carcinomas

Thorough and accurate gross examination of lumpectomy and mastectomy specimens is essential in arriving at a correct diagnosis and accurate staging for the patient. Before grossing a breast specimen, it is important to review all relevant imaging studies and know the size(s) and location(s) of the lesion(s). Figure 2-1 shows typical gross photos of a lumpectomy specimen containing an invasive breast carcinoma. Figure 2-2 shows gross photos of a mastectomy specimen containing an invasive breast carcinoma.

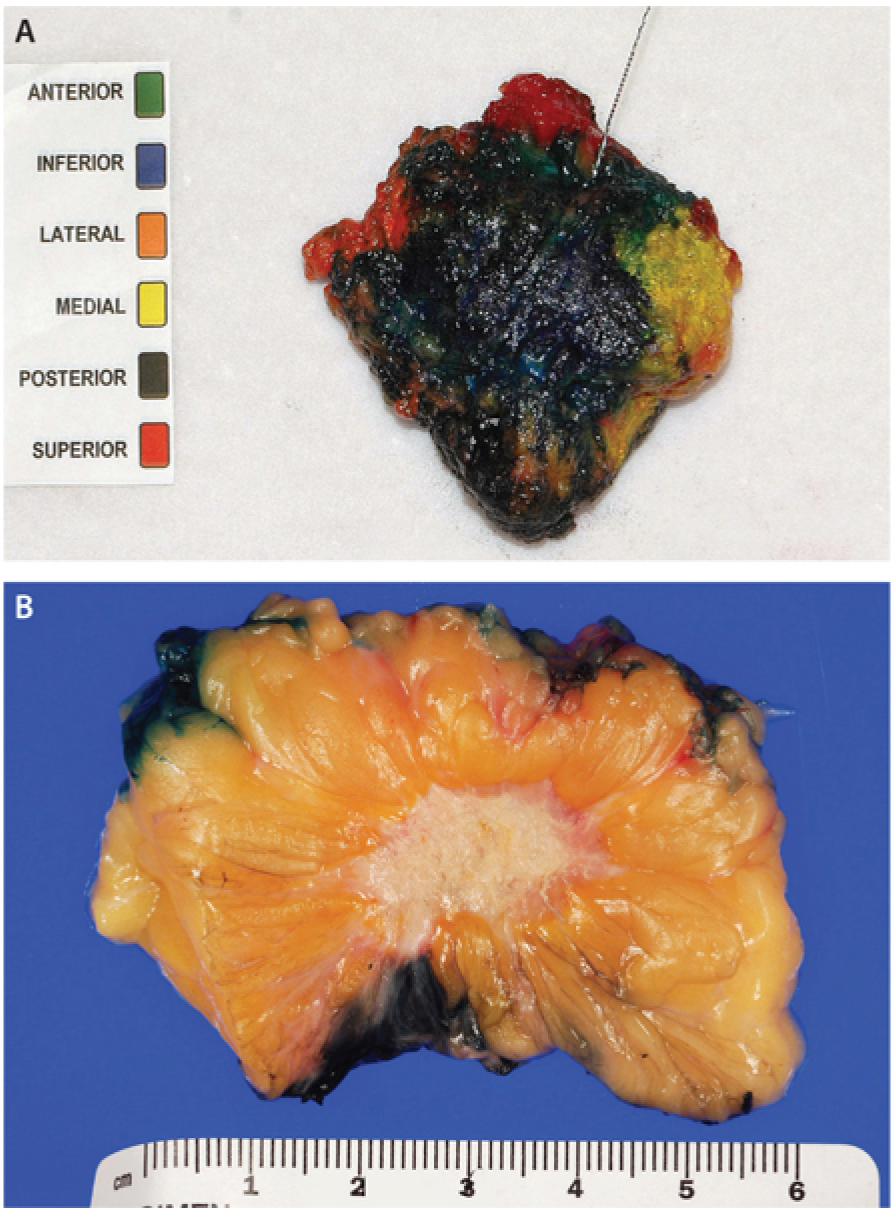

Figure 2-1. A typical lumpectomy gross specimen. Image A shows a wire-localized lumpectomy specimen that is inked with six colors for margin assessment. Image B demonstrates the cut surface of an invasive ductal carcinoma, which is firm, white, and has an irregular border.

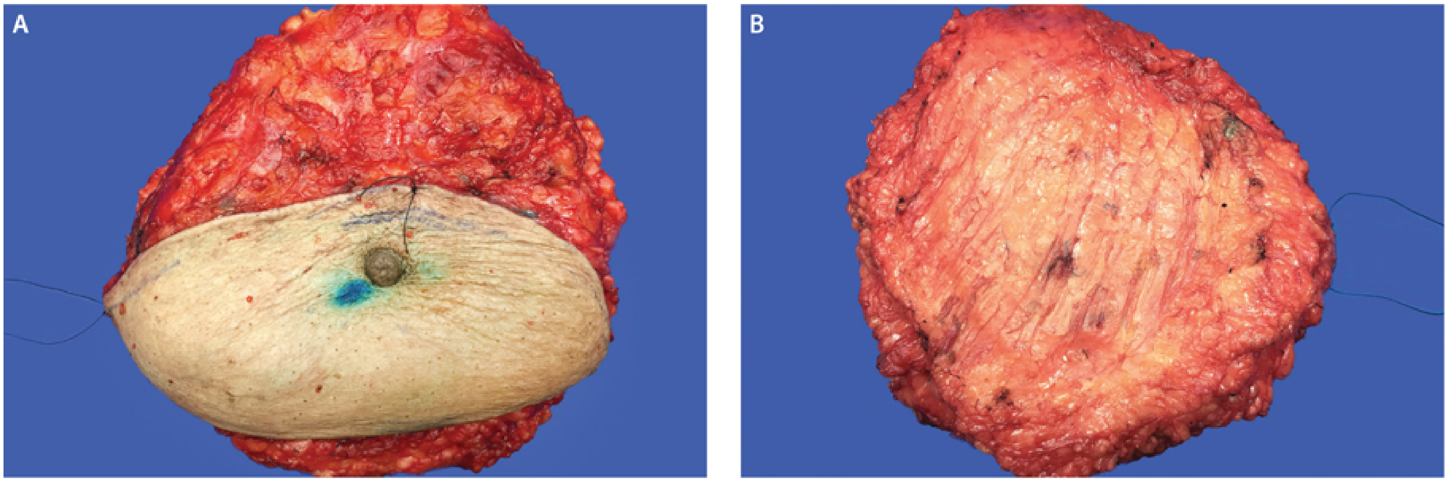

Figure 2-2. A typical total mastectomy gross specimen. Image A shows the front view of a total mastectomy specimen that includes skin and nipple. The short stitch marks the superior margin and the long stitch marks the lateral margin. Image B shows the posterior view of a total mastectomy specimen.

IV. Dissection techniques: step-by-step description

All mastectomy and lumpectomy specimens are sectioned and sampled fresh. Before grossing and dissecting a breast specimen, it is important to do the following:

1. Know if the patient has received neoadjuvant therapy.
2. Review the patient's breast-imaging studies and know the location, focus (foci), and size of the lesion(s). Know if a previous biopsy clip was placed in the tumor and if the tumor had a good response to treatment (if the patient received neoadjuvant therapy).
3. Be aware that the breast specimens should be immersed in formalin within 1 hour of removal from the patient (cold ischemic time less than 1 hour) and fixed in formalin, with an optimal fixation time of 6 to 72 hours.

Mastectomy

1. It is important to determine if the specimen is a simple/total mastectomy (no axillary tail/lymph nodes), modified radical mastectomy (includes breast and axillary tail, and a lymph node search must be performed), or a radical mastectomy (very uncommon, includes breast and axillary tail, a search for lymph nodes, and underlying pectoralis muscle). If unsure of the specimen type, it is best to talk to the breast surgeon to clarify.
2. If the specimen includes an axillary tail, make a special marking (with ink or scissors) on the skin near the axillary tail, in case there is a need to go back later and look for more lymph nodes.
3. Examine the skin and nipple, and note any abnormal findings.
4. Use a large knife to serially section the breast from the posterior surface in 2- to 3-mm intervals.
5. Go through each slice and look for tumor, any firm areas, a previous biopsy site, or a metal clip. After a visual examination, feel each slice for tumor or firm areas. Remember to correlate with radiologic findings.
6. If a tumor is identified grossly, describe the tumor location, size, and distance to all margins.
7. There is no need to ink the entire posterior margin black before sectioning because it interferes with the gross examination of the slices. Ink the margins that are close to the tumor after a tumor or a suspicious area is identified (Figure 2-3).

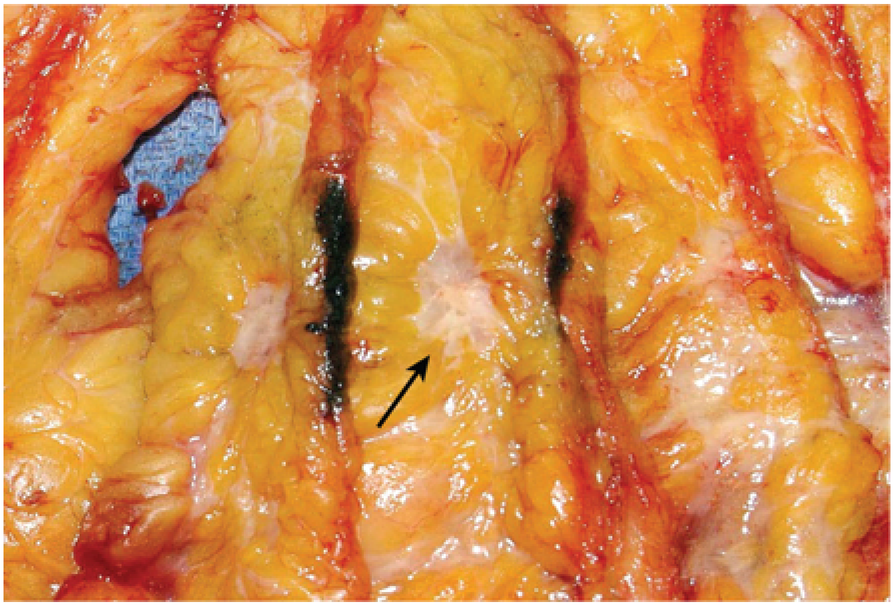

Figure 2-3. A mastectomy gross specimen with invasive ductal carcinoma. The image shows a serially sectioned mastectomy specimen from the posterior surface. A firm, gritty mass with an irregular border is present (arrow). The posterior margin of this mass is inked with black ink.

8. If a tumor is not identified grossly, especially in the setting of neoadjuvant therapy, review the preoperative imaging findings, and obtain a radiograph of the mastectomy specimen to identify the previous biopsy clip. The tumor bed usually appears as an ill-defined fibrotic area (Figure 2-4).

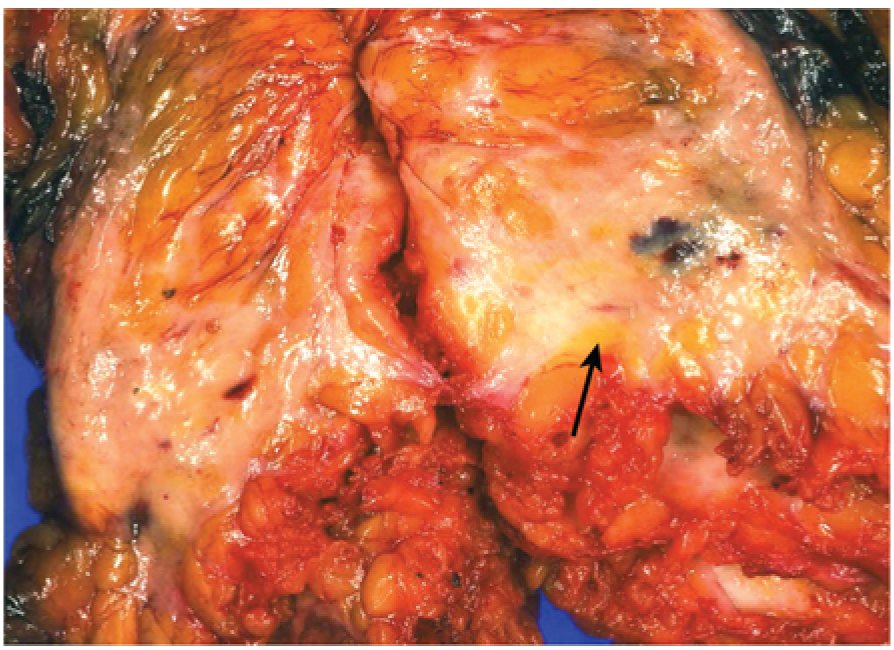

Figure 2-4. A mastectomy gross specimen with tumor bed. The image shows a serially sectioned mastectomy specimen from the posterior surface. An ill-defined fibrotic area of tumor bed is present (arrow).

9. Take the tumor sections in a sequential fashion and take a full-face section of the tumor or tumor bed[4,5] (Figure 2-5).

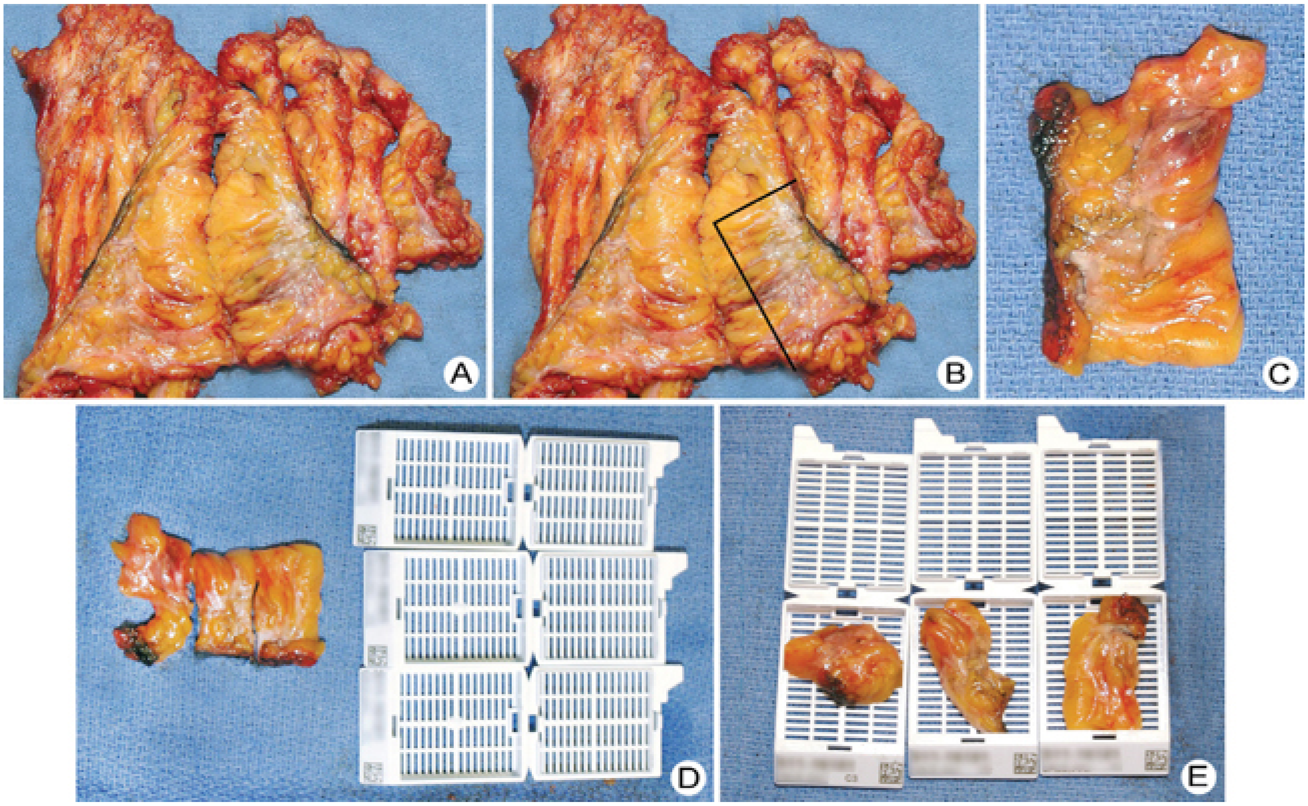

Figure 2-5. Sampling of tumor or tumor bed in a mastectomy specimen. After the specimen is serially sectioned from the posterior surface and a lesion is grossly identified, the posterior margin of the lesion is inked black (A). Block out the full face of the lesion (B and C). Submit in separate cassettes (D and E) and note in the gross description that these three blocks represent a full-face section of the lesion.

10. Submit the entire nipple (Figure 2-6).

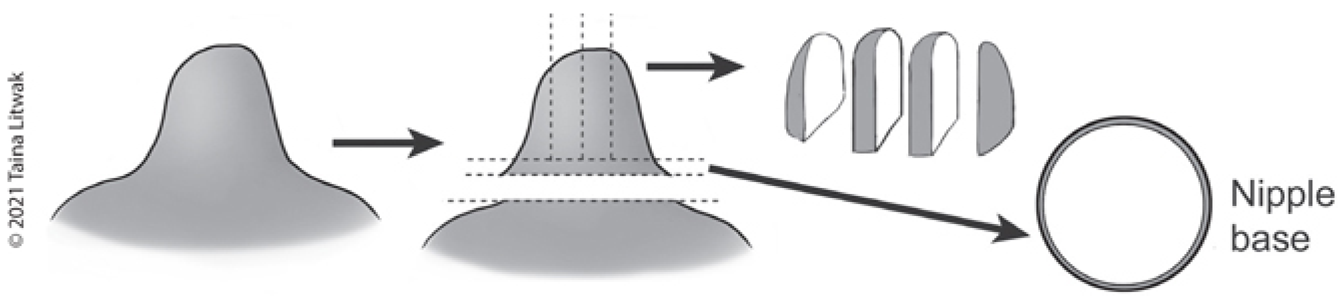

Figure 2-6. A diagrammatic illustration of how to submit the entire nipple for microscopic examination. A cross-section of the nipple bed and longitudinal sections of the nipple papillae should be submitted.

11. Submit the abnormal area of skin, if identified; otherwise, submit a representative section.

12. If the specimen contains axillary content, search for lymph nodes. Document lymph node number, size range, and gross appearance. Submit all lymph nodes.

13. Sections must be thin enough to not touch both the top and the bottom of the cassette (the thickness of a nickel). If you close the cassette and tissue is coming out of the holes in the lid, go back and trim the section down with scissors.

14. Document the time the breast was removed from the patient, placed in formalin, and then removed from formalin.

Nipple-sparing mastectomy

The surgeon usually marks the nipple bed on the nipple-sparing mastectomy specimen by sutures or clips. Shave the bed of the nipple areola complex and submit entirely in a cassette. If the section is large, it can be divided into halves or quadrants and submitted entirely. The diagnosis of the nipple bed shave should be included in the final pathology report of a nipple-sparing mastectomy.

Lumpectomy

1. After receiving the lumpectomy specimen, obtain a radiograph and confirm the presence of a previous biopsy clip or radioactive seed in the specimen (Figure 2-7A,B).

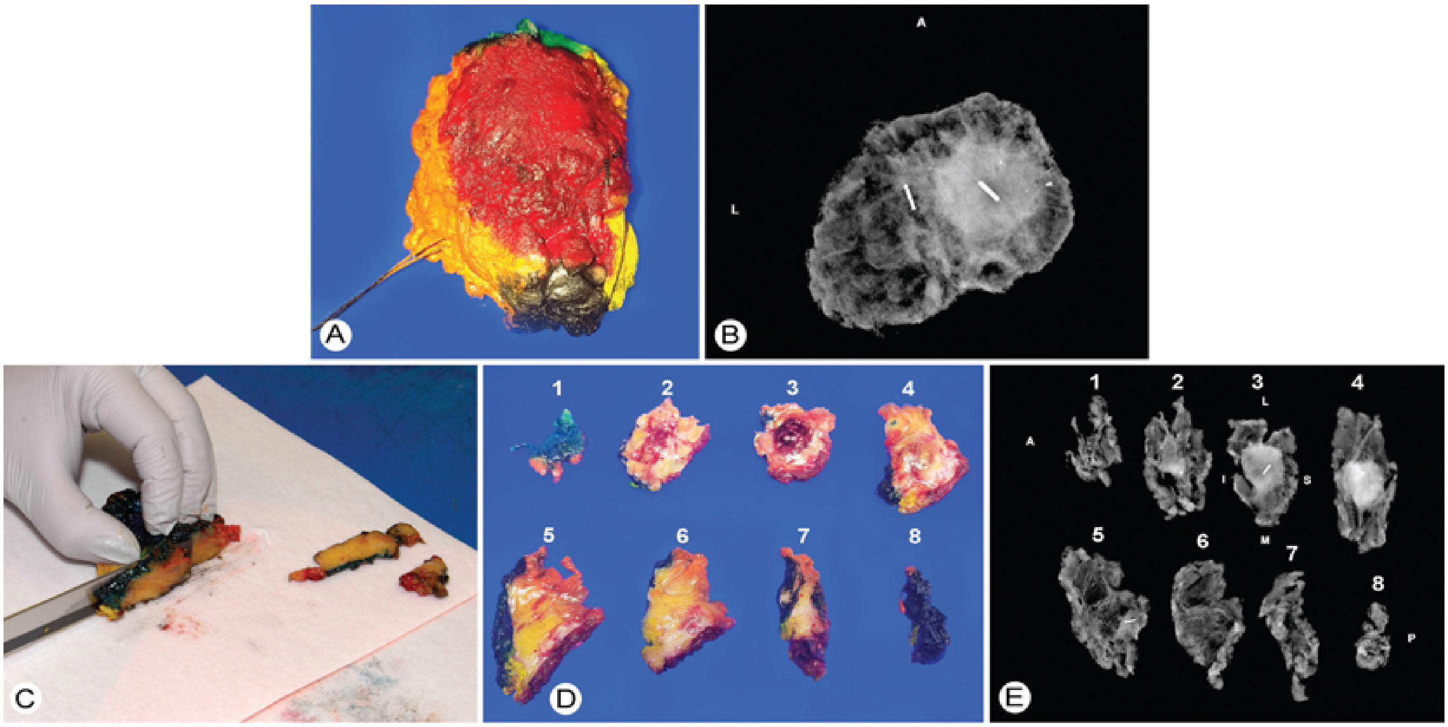

Figure 2-7. Grossing of a lumpectomy specimen. After receiving the lumpectomy specimen, ink it with six colors on six surface margins (A). Obtain a radiograph of the lumpectomy specimen (B), and document the presence or absence of clips and radioactive seeds (one biopsy clip and one radioactive seed are identified in this specimen). Serially section the lumpectomy specimen perpendicular to the long axis (C), and lay out each slice (D). Take another radiograph of the sliced specimen (E). The specimen is oriented with A (anterior), P (posterior), L (lateral), M (medial), S (superior), and I (inferior). In this case, slice #3 contains a radioactive seed, and slice #5 contains a previous biopsy clip. Describe the size, location, and distances to margins of the lesion. Submit the specimen by slices (A1, slice #1; A2, slice #2; A3-A4, slice #3, etc). The two end slices are perpendicularly sectioned and submitted as perpendicular margins.

2. If there is a wire in the specimen, carefully remove the wire and do not disrupt the specimen.

3. It is important to take time initially to determine correct orientation of the lumpectomy. Ink is then carefully applied. Ink the specimen in six colors.

4. Serially section perpendicular to the long axis, dictating which direction you do so (such as from superior to inferior or from medial to lateral) (Figure 2-7C).

5. Lay out the slices to examine the specimen. Count the number of slices and designate each piece with a slice number (Figure 2-7D).

6. Take another radiograph of the sliced lumpectomy and make a note of which slice contains the previous biopsy clip or radioactive seed (Figure 2-7E).

7. If a tumor is identified grossly, describe the tumor location, size, and distance to all margins.

8. Inform the surgeon intraoperatively about the presence and number of biopsy clips and/or radioactive seed, as well as the distance between the lesion and margins. If the lesion approaches a certain margin, re-excision of that margin is recommended intraoperatively to avoid a potential subsequent second surgery for re-excision.

9. Submit the lumpectomy specimen in a sequential fashion by slice numbers. The two end margins are sectioned perpendicularly and submitted as perpendicular margins. The other slices each contain four margins.

10. If the lumpectomy specimen is small and would fit in 25 cassettes, submit all slices.

11. If the lumpectomy specimen is large, submit representative full-face slices of tumor (one slice per 1 cm of the tumor) and any adjacent slices with suspicious areas.

12. If a tumor is not identified grossly, especially in the setting of neoadjuvant therapy, review the preoperative imaging findings, and examine the slice containing the previous biopsy clip. The tumor bed appears as an ill-defined fibrotic area. Submit the slices that contain previous biopsy sites or fibrotic areas. It may be necessary to submit the entire lumpectomy specimen.

13. Document the time the specimen was removed from the patient, placed in formalin, and then removed from formalin.

Shave margins

If shave margins are taken by the surgeon after the lumpectomy specimen, each shave margin is inked with two colors—the false margin one color and the true margin a different color. Then the shave margin is serially sectioned perpendicular to the long axis and submitted entirely for microscopic examination.

Sentinel lymph node

Examine and palpate the specimen and determine the number of lymph nodes. Separate the lymph nodes if more than one is identified, and document the size of each lymph node. Remove excess adipose tissue around the lymph node. Serially section the lymph node perpendicular to the long axis at 2-mm intervals (Figure 2-8). Submit the sections entirely for frozen section, or touch prep, or in formalin for permanent sections, according to your practice and instructions.

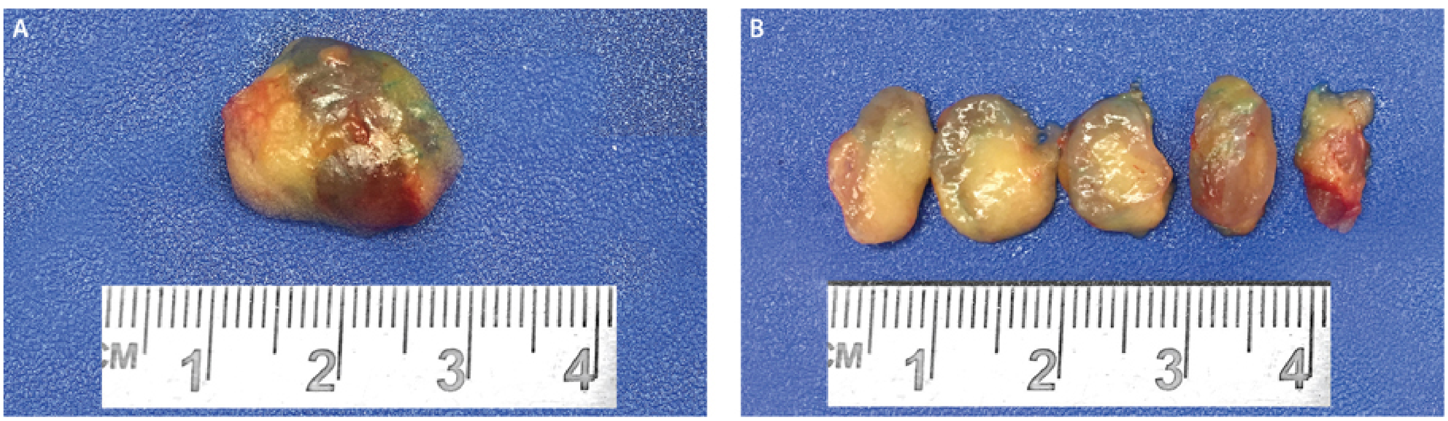

Figure 2-8. Grossing of a sentinel lymph node. After receiving the sentinel lymph node, trim away the fat around the lymph node (A). Serially section the lymph node at 2-mm intervals, and submit the node entirely for microscopic examination (B).

V. Gross descriptions using paragraph system

Gross description for a mastectomy specimen

Fixative: Fresh

Labeled: Right skin sparing mastectomy, stitch at 12:00

Specimen received: Skin-sparing mastectomy

Weight: 504 grams

Breast measurement: 18.5 cm from medial to lateral; 18.5 cm from superior to inferior; 10.2 cm from anterior to posterior

Skin appearance and size: tan-white, ellipse, 6.2 x 4.7 cm

Skin induration/retraction: No

Nipple: 1.3 x 1.3 cm, central, everted

Posterior fascia present: Yes

Fascia adherent to tumor: No
Lesion #1 size: 3.5 x 2.7 x 2.4 cm
3.7 cm from the lateral margin
11.5 cm from the medial margin
9.5 cm from the superior margin
11.3 cm from the inferior margin
1.1 cm from the anterior margin
4.0 cm from the deep margin
7.0 cm from the nipple
Lesion #1 quadrant: upper outer quadrant
Lesion #1 location: 10:30
Metallic clip identified: Yes, vision clip
Lesion #2 size: 1.6 x 1.5 x 1.3 cm
12.0 cm from the lateral margin
3.1 cm from the medial margin
11.0 cm from the superior margin
3.1 cm from the inferior margin
1.2 cm from the anterior
1.4 cm from the deep margin
5.5 cm from the nipple
Lesion #2 quadrant: Lower inner quadrant
Lesion #2 location: 3:30
Metallic clip identified: Yes, X clip
Distance between lesion #1 and lesion #2: 12.0 cm
Uninvolved breast parenchyma: Fibrous and unremarkable
Tissue sent to the Biospecimen Repository core facility: No
The deep resection margin is inked black and the anterior resection margin is inked blue.
Axillary dissection attached: No
Representative sections of the specimen are submitted as follows:
A1: Representative sections of the upper outer quadrant
A2: Representative sections of the lower outer quadrant
A3: Representative sections of the lower inner quadrant
A4: Representative sections of the upper inner quadrant
A5: Representative section of skin closest to the lesion
A6: The entire nipple, serially sectioned
A7-A8: The most medial complete full-face section of lesion #1
A9-A10: The next sequential full-face section of lesion #1
A11-A12: The most lateral full-face complete section of lesion #1
A13-A14: Tissue between lesion #1 and lesion #2
A15-A16: The most medial full-face complete section of lesion #2
A17-A18: The next sequential full-face section of lesion #2
A19-A20: The most lateral complete full-face section of lesion #2

The breast is removed from the patient at 11:20 on date/2020, placed in formalin at 12:17 on date/2020, and not removed from formalin until 20:14 on date/2020.

Gross description of a lumpectomy specimen

Fixative: fresh
Labeled: Right lumpectomy at 10:00, one clip, one radioactive seed

Measurement: 2.1 cm from superior to inferior; 2.8 cm from medial to lateral; 1.5 cm from anterior to posterior

The specimen is inked as follows:

Inferior: blue

Anterior: green

Posterior: black

Lateral: orange

Medial: yellow

Superior: red

Sectioned from: medial to lateral

Total number of slices: Six

Radioactive seed: Yes, slice #5

Metallic clip: Yes, slice #5, open coil clip

Mass/lesion measurement: 0.8 x 0.7 x 0.6 cm

Mass location: slice number 3 through 5

The mass is:

0.3 cm from the posterior margin

0.3 cm from the anterior margin

0.6 cm from the lateral margin

1.0 cm from the medial margin

0.7 cm from the superior margin

0.6 cm from the inferior margin

Uninvolved breast parenchyma: 50% tan-white and fibrous; 50% yellow ad lobulated

Specimen radiograph taken: Yes

Specimen sent to the Biospecimen Repository core facility: No

The entire specimen is/representative sections are] submitted as follows:

A1: Slice #1, perpendicular medial margin

A2: Slice #2

A3: Slice #3

A4: Slice #4

A5: Slice #5

A6: Slice #6, perpendicular lateral margin

The breast is removed from the patient at 0802 on date/2020, placed in formalin at 0821 on date/2020, and not removed from formalin until 20:14 on date/2020.

VI. Common pathologic findings in lumpectomy and mastectomy

Specimens without neoadjuvant treatment

- Invasive ductal carcinoma with or without adjacent ductal carcinoma in situ (Figure 2-9A)
- Different histologic types of invasive carcinoma, including invasive lobular carcinoma, mucinous carcinoma, and micropapillarycarcinoma (Figure 2-9B-D)
- Lobular carcinoma in situ, atypical lobular hyperplasia, atypical ductal hyperplasia
- Benign changes, including papillomas, radial sclerosing lesions, and fibrocystic changes

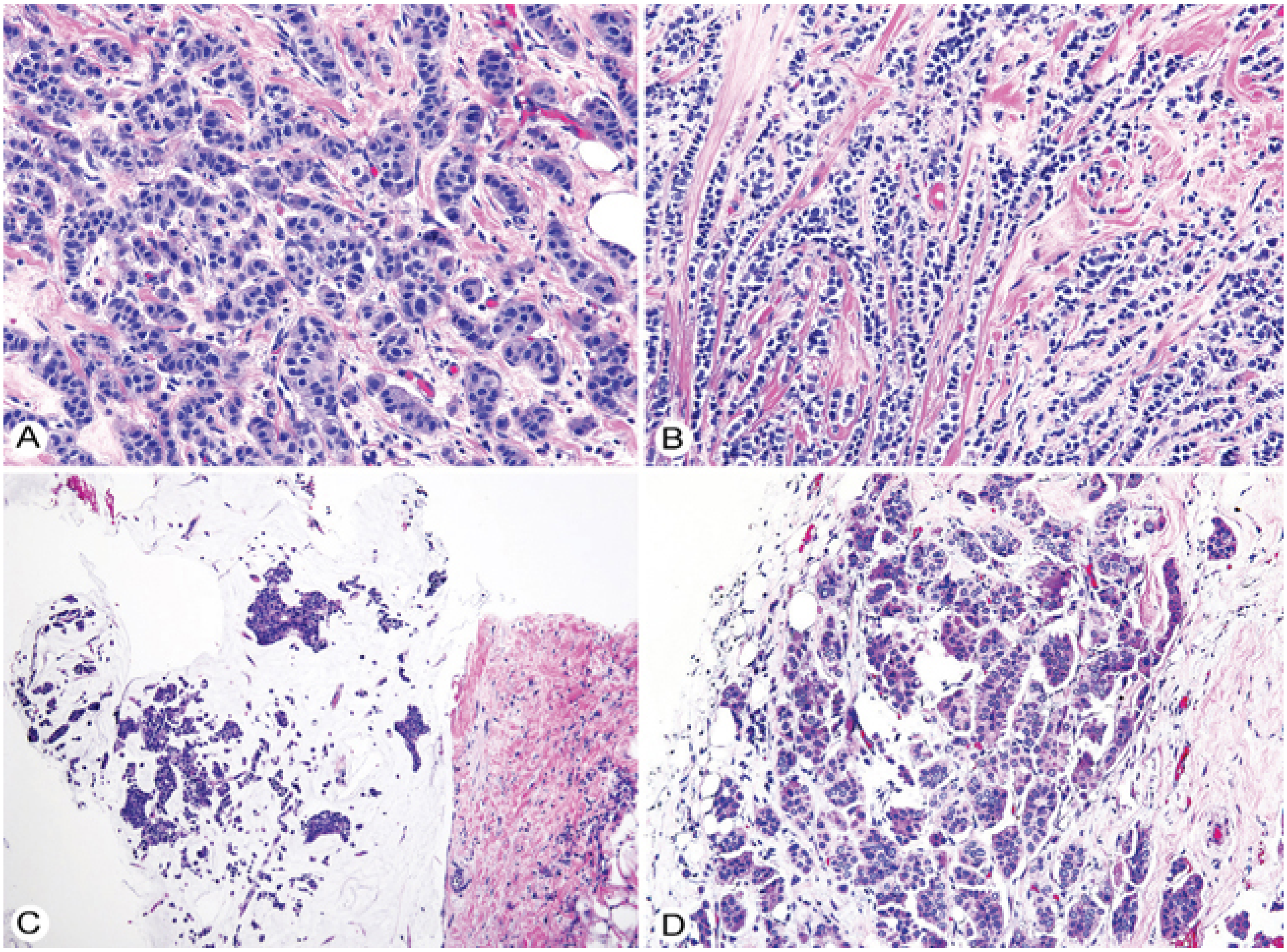

Figure 2-9. Microscopic images of invasive breast carcinomas, including invasive ductal carcinoma (A), invasive lobular carcinoma (B), mucinous carcinoma (C) and micropapillary carcinoma (D) (H&E sections, x100).

Specimens with neoadjuvant treatment

- Tumor bed showing hyalinized stroma, edema, fibroelastosis, patchy aggregates of lymphocytes, foamy histiocytes, and hemosiderin deposition (Figure 2-10A,B)
- Residual in situ and invasive carcinomas (Figure 2-10C,D)
- Most residual invasive carcinomas do not show changes in morphology as compared with pretreatment tumor. Some may show marked retraction artifact.

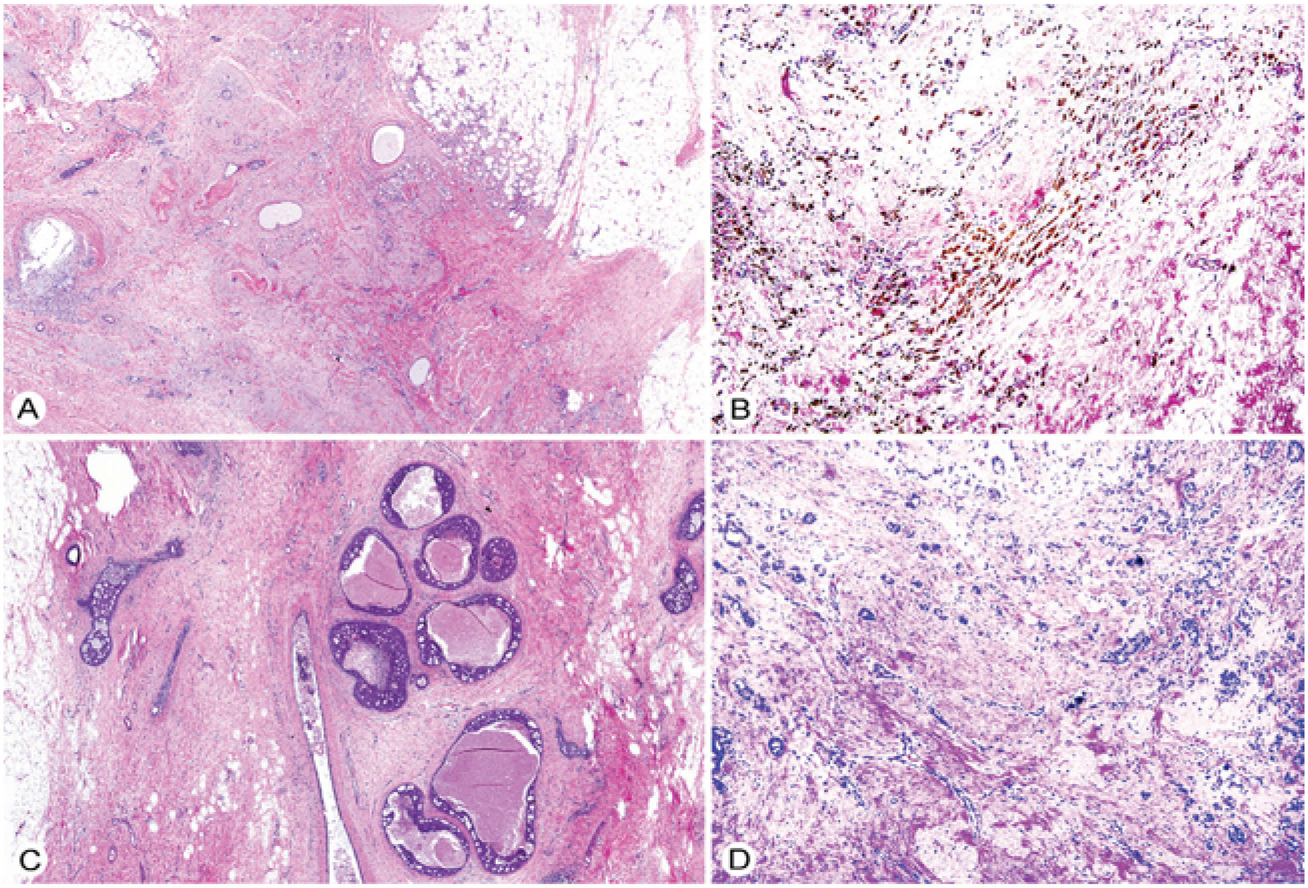

Figure 2-10. Microscopic images of breast carcinoma after neoadjuvant treatment. The tumor bed shows hyalinized stroma, edema, fibroelastosis (A, H&E, x100), patchy aggregates of lymphocytes, foamy histiocytes, and hemosiderin deposition (B, H&E, x200). Image C shows a tumor bed with residual ductal carcinoma in situ only, with no invasive carcinoma identified (C, H&E, x200). Image D shows residual invasive carcinoma and a background of treatment effect (D, H&E, x100).

VII. Common potential staging pitfalls and solutions T staging

1. The size of the invasive carcinoma is used in the T staging; therefore, the accuracy of the measurement is important. Always correlate microscopic findings with gross measurement and radiologic measurement to ensure accurate size designation. The size is for the invasive carcinoma only and therefore should not include the adjacent ductal carcinoma in situ (DCIS).[6]

2. When there are multiple, separate foci of invasive carcinoma, the size of the largest focus is used for T staging. Do not add the sizes together from multiple foci. Use TNM descriptor m (for multiple foci) in the pathologic TNM (pTNM) staging, such as "pmT1b."

3. If the size of the invasive carcinoma is larger in the previous core needle biopsy specimen than in the excision specimen (lumpectomy or mastectomy), the size in the prior biopsy specimen should be used for T staging. Do not add the sizes together.

4. For any invasive carcinoma larger than 1.0 mm but less than 1.5 mm, the size should be rounded up to 2.0 mm to ensure that the tumor is categorized as pT1a, not pT1mi.[7]

5. Skin involvement[7]:

- Direct skin involvement by an underlying invasive carcinoma without skin ulceration should not change the T stage. Tumor is staged according to the tumor size.
- Direct skin involvement by an underlying invasive carcinoma with skin ulceration should be staged as pT4b.
- Grossly identified satellite skin nodule of invasive carcinoma (not contiguous with the main tumor) should be staged as pT4b. Satellite skin nodules identified microscopically do not qualify as pT4b.

6. Pectoralis muscle involvement is not considered chest wall invasion and should not be staged as pT4a. Such tumors should be staged based on tumor size.

N staging

1. When there are multiple clusters of tumor cells present in a lymph node, the size of the largest contiguous focus is used to stage the lymph node.

2. When tumor cells show a dispersed pattern of lymph node involvement, such as metastatic lobular carcinoma, it is difficult to estimate the size of metastasis. The pathologist's judgment is required in such cases to avoid underclassification.[8]

3. After neoadjuvant therapy, any residual carcinoma in the lymph node is considered node positive; hence, use of the term *isolated tumor cells* should be avoided in this setting.[9]

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

- Description of procedure performed and tissue/organ present
- Description of type of tumor: Is tumor in situ or invasive?
- If invasive, indication of any morphologic variant and histologic grade
- Tumor location and size
- Tumor margins
- Presence of lymphovascular invasion
- Number of lymph nodes examined (if applicable), and number that are positive

If the patient has received neoadjuvant therapy, the following additional information should be included in the pathology report[9,10]:

- Size and location of tumor bed
- Size and location of residual tumor
- Cellularity of residual tumor
- Presence/absence of treatment response in the lymph nodes with metastases
- Number of lymph nodes showing evidence of treatment response by no residual tumor

A sample report is provided below to demonstrate the necessary information to be included in a pathology report, including a synoptic report.

Final diagnosis

Breast and axillary lymph nodes, right, modified radical mastectomy:

- Invasive ductal carcinoma, histologic grade II, located in the upper outer quadrant (10:00, 5 cm from the nipple), 1.8 cm in size
- Lymphovascular invasion present
- Ductal carcinoma in situ, intermediate nuclear grade
- Margins negative for involvement
- Skin and nipple unremarkable
- 18 axillary lymph nodes, negative for metastatic carcinoma (0/18). See synoptic report.

Synoptic report

The following information is a modification of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*[6] and College of American Pathologists (CAP) cancer protocol for invasive carcinoma of the breast.[7]

Specimen Type: Modified radical mastectomy

Laterality: Right

Tumor Site: 10:00, 5 cm from the nipple

Histologic Type: Invasive ductal carcinoma, no special type (NST)

Size of Invasive Component: 1.8 x 1.2 x 0.9 cm

Tumor Multicentricity: Absent
Surgical Margins:
For invasive carcinoma: More than 2 mm from all margins
For DCIS: More than 2 mm from all margins
Histologic Grade (Nottingham Histologic Score): II/III
Tubule Formation: 3
Nuclear Grade: 2
Mitotic Count (40x objective): 1
Total Nottingham Score: 6/9
Ductal Carcinoma In situ (DCIS): Present
Extensive intraductal component (>25%): Absent
DCIS within and/or adjacent to invasive carcinoma: Yes
DCIS separate from invasive carcinoma: No
Lymph-Vascular Invasion: Present
Nipple Involvement: Absent
Skin Involvement: Absent
Skeletal Muscle: Not present
Lymph Node Sampling:
Axillary dissection
Total number of involved nodes/total nodes found: 0/18
Number of lymph nodes with macrometastases (>2 mm): 0
Number of lymph nodes with micrometastases (>0.2 mm to 2 mm): 0
Number of lymph nodes with isolated tumor cells (<0.2 mm and <200 cells): 0
Prognostic markers: Ordered. The results will be issued as an addendum.
Time between tumor removal and placement into formalin < 1 hour: Yes
Fixation Time between 6 and 72 hours: Yes
Pathologic Staging (AJCC 8th edition):
pT1cN0Mn/a

The pathologic stage assigned here should be regarded as provisional because it reflects only current pathologic data and does not incorporate full knowledge of the patient's clinical status and/or prior pathology.

Block for Biomarker Testing: [A12]

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3. Central Nervous System

Mark E. Jentoft, MD; Aditya Raghunathan, MD, MPH

Introduction

In most organs of the body, orientation of a tumor or disease process to the remainder of the organ can be readily performed at the time of gross assessment of the tissue. The central nervous system (CNS) is somewhat unique, in that the extent of neurosurgical excision is dictated by the structures involved and what can be removed with minimal adverse neurological consequences to the patient, resulting in only minimal normal/uninvolved tissue being removed. Additionally, the excised tissue is often fragmented, especially when the cavitational ultrasonic surgical aspirator (CUSA) is utilized. Consequently, the orientation and size of the lesion is typically difficult to determine at the time of gross examination and is often deferred to the preoperative radiographic (magnetic resonance imaging ([MRI]/computed tomography [CT]) findings. Also, unlike many other sites, analysis of the extent of resection and involvement of margins typically is not performed; instead, these assessments are based on the surgical and postoperative radiographic impressions. As noted in the American Joint Committee on Cancer (AJCC) 8th edition staging system, the stage of the tumor in neurosurgical specimens does not have a predictive factor similar to other organs; rather, the histologic type, grade, and genomic features of the tumor play a greater role in prognosis and predicted response to therapy.[1] It is increasingly important that sufficient quantity of neoplastic tissue is present, in order to perform appropriate characterization, including not only immunohistochemical stains, but also appropriate additional molecular testing.

Intraoperative analysis of CNS tissue may employ cytologic preparations and/or frozen sections. Cytologic preparations are typically preferred when the volume of tissue submitted for intraoperative analysis is small, such as from stereotactic biopsies, and may include touch preparations, "squash" preparation, or tissue smears. Frozen section analysis is preferred by many pathologists when abundant tissue has been submitted or when the tissue appears firm or fibrotic. The decision to perform frozen section analysis on CNS tissue must be taken with caution, as CNS lesions are often associated with edema, and freezing may cause significant artifactual distortion at the time of intraoperative evaluation, as well as in the subsequently processed permanent sections, which may severely limit histologic interpretation as well as immunohistochemical evaluation of the previously frozen tissue. This being noted, cytologic preparations are also vulnerable to a variety of artifactual distortions, including air drying and the Azzopardi effect.

Cytologic preparations can be very helpful in forming diagnoses based on the morphology of tumor cells. Nuclear and cytoplasmic features, such as chromatin texture and the fibrillary nature of cytoplasmic processes, are very useful in determining the lineage of the cells of interest and may not be as readily appreciated on frozen sections. This being noted, overall tissue architecture and growth patterns of neoplasia are often more apparent on frozen sections. For example, the presence of perivascular pseudorosettes in ependymoma often is easily seen in frozen sections but may be difficult to appreciate in cytologic preparations. Additionally, frozen sections may also allow more accurate assessment of overall cellularity, while such an assessment may be less reliable in cytologic preparations due to highly variable quantities of tissue being utilized.

One significant consideration when submitting small biopsy fragments is the potential for artifactual distortion, which may severely limit morphologic assessment. Potential sources of such distortion include excessive pressure being applied by the forceps used to transfer the tissue out of formalin into the cassette. The use of biopsy bags or sponges to ensure preservation of the small biopsy fragments is another common source of inadvertent tissue distortion. Instead, carefully wrapping the tissue in lens paper serves to preserve tissue through processing while minimizing artifacts introduced through grossing. With small biopsies, placing an order for unstained sections in addition to the routine hematoxylin-eosin–stained section at the time of grossing

may reduce the possibility of exhaustion of paraffin-embedded tissue and allow for molecular evaluation, even though tissue may appear limited.

Though electron microscopy (EM) may be performed on formalin-fixed paraffin-embedded tissue, the quality of ultrastructure preservation tends to be better if small portions of tissue are placed in more appropriate fixative for performing EM (like glutraldehyde). In most circumstances, there is limited utility of EM to establish a diagnosis. However, EM can be very useful in certain challenging circumstances, such as supporting ependymal or Schwannian differentiation, when it is not otherwise apparent. Traditionally, EM was also used in the analysis of pituitary adenomas; however, immunohistochemical staining to assess pituitary hormones and transcription factors (Pit-1, SF-1, and Tpit) has all but replaced the utility of EM in these. The role of EM is further limited by the ever increasing utilization of molecular testing to help classify, prognosticate, and direct therapy of primary CNS tumors.

An in-depth review of the classification of CNS tumors is beyond the scope of this chapter. Instead, we will focus on some basic principles to guide handling CNS specimens and formulating diagnoses based on integrating clinical, radiologic, histologic, and molecular findings.

I. Common tumors from the brain and spinal cord and grossing techniques

A wide range of tumors may be present within the brain and spinal cord parenchyma. Often, the amount of tissue biopsied is small, and the entire tissue may be submitted for histologic assessment. In other circumstances, abundant tissue may be resected and only representative sections may be submitted for evaluation. Extreme caution must be exercised while handling samples from particularly sensitive areas of the CNS, such as the brainstem, spinal cord, pineal region, and deep brain nuclei, since often only limited tissue will be obtained, and repeat surgery may be impossible due to the high risk of adverse clinical consequences. In such cases, it is paramount to understand the clinical situation, key therapeutic decisions, and the priority of tests that may be required, in order to utilize the tissue in the most appropriate manner. How you approach a limited biopsy may be drastically different based on whether the targeted lesion is suspected to be a glioma, a lymphoma, a germ cell tumor, or a metastasis.

For larger resection specimens, care must be taken to adequately sample regions of heterogeneity within the tumors. The presence of tumor necrosis will change the grade of certain CNS tumors, as can regions of elevated proliferative activity, hypercellularity, and abnormal vasculature. Areas of gross transition in tissue density and color should be sampled. Additionally, it is important to determine the growth pattern of a tumor by evaluating the interface between the neoplasm and adjacent nonneoplastic parenchyma, as the differential diagnostic considerations, testing required, grading, and therapy are different if a tumor has infiltrative growth, such as in diffuse astrocytoma, or if it is more circumscribed, such as in pilocytic astrocytoma. The junction between the cortex and white matter, and presence of overlying leptomeninges, often can be grossly appreciated in larger resection specimens. For these cases, it is optimal to take sections perpendicular to the grey-white junction and try to include overlying meninges, as this allows for microscopic analysis of how the tumor is related to the cortex and white matter. In certain tumors, such as a dysembryoplastic neuroepithelial tumor, appropriate orientation will greatly assist with definitive diagnosis.

Dura-based lesions

The most common primary dura-based tumor is a meningioma. It is important for dura-based tumors to be adequately sampled, as higher grade components may be embedded within a predominantly low-grade lesion. Adherent brain parenchyma may occasionally be included in these resections, and it is imperative to sample the tumor-brain interface, as it may reveal invasion of the brain parenchyma by the dural tumor. Occasionally, the examination of adherent-appearing brain parenchyma might disclose the tumor to represent gliosarcoma (a variant of glioblastoma), which may involve the meninges, and may have been favored to represent a dural mass with underlying edema in preoperative imaging studies. Sampling of identifiable brain parenchyma in these cases will facilitate identification of a malignant glial component, in the absence of which the diagnosis can be extremely challenging.

Sella/pituitary lesions

A variety of lesions may involve the region of the sella, the most common by far being pituitary adenoma. However, the diagnosis of an adenoma may be challenging, such as when the diagnostic region is minute (ie, a microadenoma), or a very large adenoma has undergone hemorrhage and necrosis. If intraoperative evaluation is requested, cytologic preparations (touch imprints or smears) are often adequate. The normal pituitary gland is composed of admixtures of anterior pituitary cells showing acidophilic, basophilic, and chromophobe cytoplasm, arranged as nests of varying sizes, surrounded by a rich reticulin network. In contrast, the nested reticulin architecture is disrupted in adenomas. This disruption of the reticulin network often allows for ready diagnosis by cytologic preparations that show abundant, cytologically uniform adenoma cells. Although frozen sections may be performed when adequate tissue is available, artifactual distortion may hinder intraoperative assessment, and subsequent processing for permanent sections may result in loss of diagnostic regions, particularly for microadenomas.

In addition to adenomas, a variety of cystic lesions may arise in the sellar region, such as the craniopharyngioma variants (adamantinomatous and papillary) and Rathke cleft cysts. Adequate sampling of cyst contents, if present, may help establish the diagnosis. Finally, a spectrum of inflammatory and neoplastic lesions arising in adjacent nasopharynx or bone may present as masses involving, or even apparently centered in, the sella. Typically, submission of resected tissue in its entirety can help identify the tissue of origin.

Nonneoplastic brain lesions

Biopsies at times may be performed for nonneoplastic conditions such as seizures, white matter diseases, or encephalitis. In these cases, the possibility of a prion disorder, such as Cretzfield-Jakob disease (CJD), should be considered before tissue processing. If a prion disorder is a clinical and/or radiologic consideration, even if only as a remote possibility, adequate precautions must be exercised to prevent possible disease transmission. This includes utilizing disposable instruments and adequately denaturing the prion protein, by first fixing small pieces of the tissue in formalin, then treating the tissue with 95% formic acid for an hour, before transferring the tissue back into formalin for histologic processing. Additionally, a portion of the tissue should be frozen at -80°C for Western blot analysis, which may be essential for confirming and subtyping prion disease and can be performed by The National Prion Disease Pathology Surveillance Center in Cleveland, Ohio. More complete details on tissue processing and laboratory instrument decontamination for suspected prion cases can be found in the document, WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies.[2]

Resections performed for medically refractory seizures may range from amygdalohippocampectomy to removal of a cortical seizure focus identified by imaging studies or electroencephalography. In these cases, it is important to attempt to obtain coronal sections of the hippocampus and sections perpendicular to the cortical surface in order to allow for optimal assessment of both hippocampal and cortical architecture. The orientation of partial or complete hippocampectomy specimens begins with locating the smooth, glistening surface with few thin veins, which represents the ventricular lining of the temporal horn of the lateral ventricle, and identifying a groove representing the junction of the medial and lateral walls of the temporal horn. Sectioning perpendicular to this groove will allow coronal orientation of the hippocampus proper, enabling optimal assessment for hippocampal sclerosis. For the resections of the cortex, orientation is much simpler, based on identifying the smooth superficial surface showing gyri, sulci, and leptomeninges. Additionally, the cortical-white matter transition is often apparent on the cut surfaces and can also aid in orientation. Sectioning perpendicular to the surface of gyri allows for optimal analysis of the radial and tangential architecture of cortical layers and the transition between the cortex and white matter—key to the assessment of cortical dysplasia.

II. What to include in the pathology report

The 2016 *WHO Classification of Tumours of the Central Nervous System* incorporates histologic and genetic information into an integrated diagnosis for several entities, including instances where the molecular/cytogenetic findings trump morphology for defining the tumor entity.[3] For instance, oligodendroglioma is now defined by the concurrent presence of an *IDH* mutation and 1p/19q codeletion in an

infiltrating glioma, regardless of the nuclear morphology seen on histologic sections. Depending on the tests required for a particular case, this may result in a long turnaround time between surgery and assigning a final diagnosis when all of the information becomes available. Additionally, in many institutions, the required molecular and cytogenetic testing may not be available, and tissue needs to be sent to a reference laboratory for testing, further increasing the turnaround time. In order to help guide patient care in the interim, a preliminary diagnosis may be rendered while the required tests are being performed. It has therefore been recommended that a layered report be issued for cases requiring molecular and/or cytogenetic information for the diagnosis of the entity, as available information can be reported in an organized fashion over time. These reports contain four components or layers to include:

Layer 1: Integrated diagnosis

Layer 2: Histologic classification

Layer 3: WHO grade

Layer 4: Molecular information

A good resource for guidance on how to structure a neuropathology report can be found in a paper issued by the International Society of Neuropathology.[4] As an example, an oligodendroglioma, *IDH*-mutant and 1p/19q codeleted would have the following layered report:

Layer 1, Integrated Diagnosis: Oligodendroglioma, *IDH*-mutant and 1p/19q codeleted

Layer 2, Histologic diagnosis: Oligodendroglioma

Layer 3, WHO grade: II

Layer 4, Molecular information: IDH1-R132H positive immunohistochemistry and whole arm deletions of 1p and 19q detected by chromosomal microarray

Additionally, the College of American Pathologists (CAP) Protocol for the Examination of Specimens from Patients with Tumors of the Central Nervous System provides a template and discussion on how to report cases and may be found on the CAP website (www.cap.org/cancerprotocols). Of note, at times the small size of the biopsied tissue, low tumor cellularity, and exhaustion of the tissue during assessment of the case may result in inadequate tissue for performing diagnostic molecular tests. In such cases, the morphologic diagnosis alone may serve as the integrated diagnosis, with an "NOS" (not otherwise specified) designation in place of the genetic information in the diagnosis. For instance, the diagnosis oligodendroglioma, NOS, WHO grade II should be issued in a case with the classic morphology of an oligodendroglioma, wherein definitive evaluation of the *IDH* mutation and/or 1p/19q-codeletion status cannot be completed.

The understanding of CNS tumor genetics is ever changing and evolving at an increasingly rapid rate, far outpacing the time intervals between WHO editions. In order to address this, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) has been formed, with the goal "to facilitate input and consensus review of novel diagnostically relevant data and determine how such information can be practically incorporated into future CNS tumor classifications."[5] The formation of this consortium allows for consensus recommendations, which can keep pace with discoveries and novel insights in the time interval between editions of the WHO classification system for CNS tumors. To date, cIMPACT-NOW has issued multiple updates for clarification of terminology and recommendation of diagnostic criteria.[6-10]

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4. Adrenal Gland

Sylvia L. Asa, MD, PhD

Adrenal resection specimens include biopsy, laparoscopic adrenalectomy, routine open adrenalectomy and radical nephrectomy with adrenalectomy specimens.

Pathologic examination is the gold standard for elucidating the pathologic process, which will determine the management of the patient. In patients with malignant tumors, it is the basis for carcinoma staging, which offers critical information for the prognosis, therapeutic choices, and future care. Bilateral adrenalectomy may constitute the therapy for intractable hormone excess.

Appropriate handling of the specimen serves as the foundation for the diagnostic and staging process. The pathology report is not only a medical but also a legal document for future therapeutic protocols. Pitfalls exist when difficult settings are encountered. We will discuss in detail appropriate specimen handling, microscopic evaluation, and the pertinent information to include in the pathology report.

I. Indications for adrenal resections

Adrenal biopsy is performed to diagnose an adrenal lesion of unknown type. Most patients with primary adrenal lesions do not undergo this procedure because biochemistry and imaging identify the nature of their pathology. Patients with pheochromocytoma should not undergo biopsy because of the high risk of complications, and those with cortical lesions do not usually have a biopsy because the distinction of benign from malignant is usually not possible on biopsy. This procedure is primarily used to diagnose metastatic malignancy from another primary site, infiltrative lesions, or inflammatory lesions.

Adrenalectomy is the procedure undertaken to remove adrenal lesions that may be benign or malignant. Small nodules, cysts, and tumors with low risk of malignancy may be resected through a laparoscopic approach. Ideally, they can be resected intact, but sometimes they must be morcellated for removal through a limited incision. Large lesions and those suspicious of malignancy are usually resected using the conventional approach so they can be removed intact and with surrounding fat. Very large malignancies are usually resected along with the adjacent kidney.

Bilateral adrenalectomy is a therapeutic procedure that is used to reduce hormone excess, most often in patients with pituitary or ectopic adrenocorticotropin hormone (ACTH) excess. Occasional patients with germline disorders causing primary adrenal hyperfunction undergo this procedure.

II. What do we expect to see in an adrenal resection specimen macroscopically and microscopically?

The adrenal biopsy is used to identify metastatic malignancy, infiltrative lesions, or inflammatory lesions. These are not usually distinguishable grossly; therefore, microscopy is required, often with special stains and/or immunohistochemistry.

Adrenalectomy specimens usually consist of an adrenal gland with a nodule that can be of cortical or medullary origin.[1] These may be myelolipoma, pheochromocytoma, ganglioneuroma, neuroblastoma, or a composite medullary lesion, cortical adenoma, or cortical carcinoma. Occasional specimens yield a cyst, pseudocyst, or an inflammatory lesion. Exceptionally rare primary melanomas have been described. The nontumorous adrenal is also important to document because it may show cortical atrophy or hyperplasia of the cortex or medulla.

Bilateral adrenalectomy specimens usually exhibit diffuse and/or nodular hyperplasia. Those with ACTH excess have diffuse hyperplasia with lipid depletion. Some have this change superimposed on preexisting nodular adrenal cortex. Those with germline alterations usually have nodular hyperplasia or, more accurately, multifocal adenomas; occasional patients have a more dramatic form known as *macronodular adrenal*

hyperplasia. Rare examples from patients with Carney complex exhibit primary pigmented nodular adrenal cortical disease (PPNAD).

III. Typical gross photos of adrenal resection specimens

Gross diagnosis based on macroscopic observation is critical. It includes two major components: the normal adrenal gland and the lesion.

In every sample it is important to identify and describe the appearance of the nontumorous adrenal as well as the relationship between lesions and the normal gland. The normal adrenal is illustrated in Figure 4-1. Cortical hyperplasia should be recognized and described, along with the color of the tissue that reflects the functional status of the gland (Figure 4-2). Medullary hyperplasia also can be recognized grossly.[2] The recognition of atrophy of the nontumorous cortex associated with an adrenal cortical tumor (Figure 4-3) is a feature that has clinical consequences and should be reported immediately.[3] It is important to ensure that nontumorous adrenal is submitted for microscopic examination.

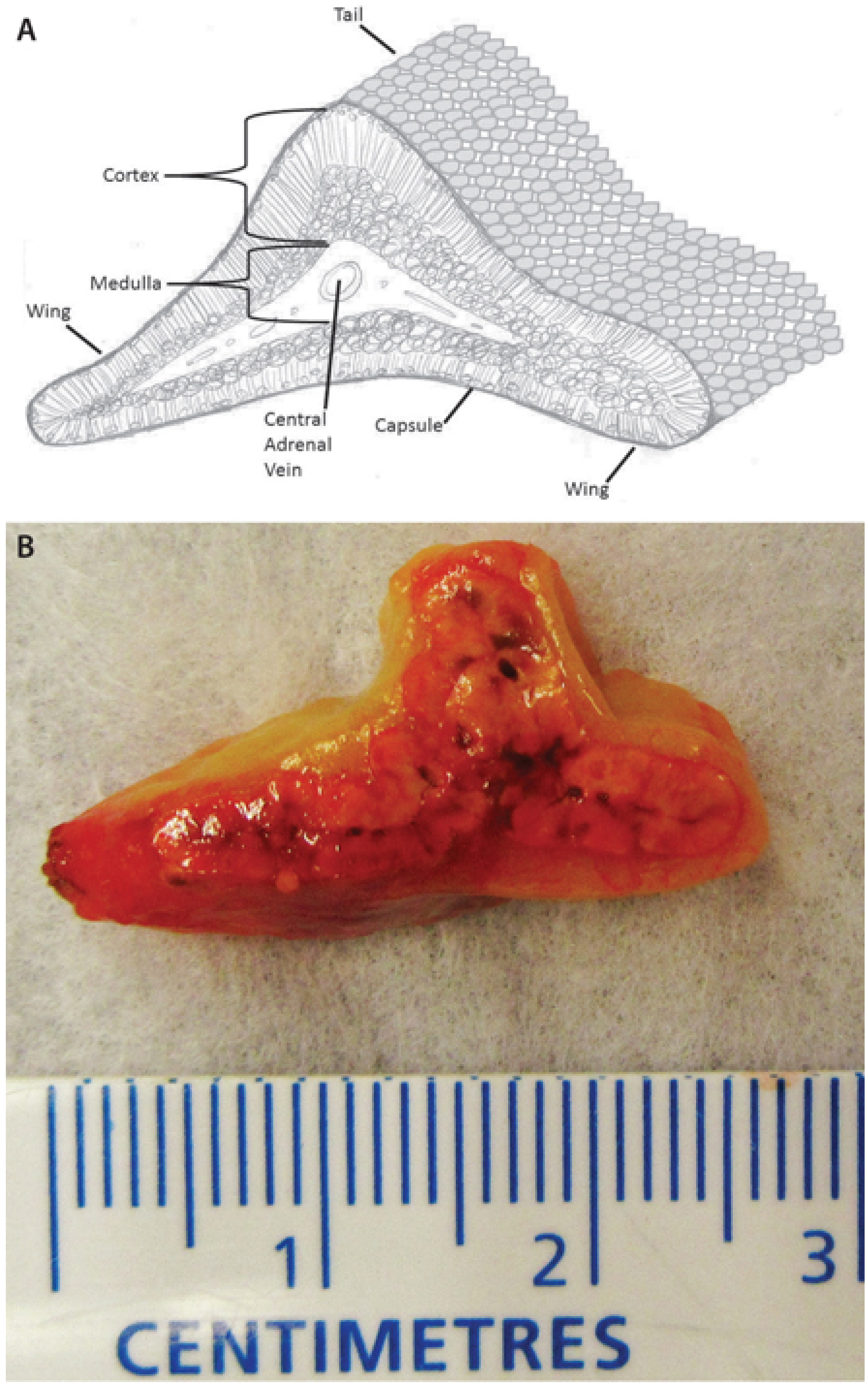

Figure 4-1. The normal adrenal gland. A. Schematic depiction of the orientation and landmarks of a normal adrenal gland. B. Gross photograph of a normal adrenal gland.

Figure 4-2. Gross photograph of a hyperplastic adrenal gland. A patient with unresectable and refractory pituitary Cushing disease underwent bilateral adrenalectomy to reduce the cortisol excess. Note the slightly thickened cortex that has a dusky brown appearance rather than a bright yellow color.

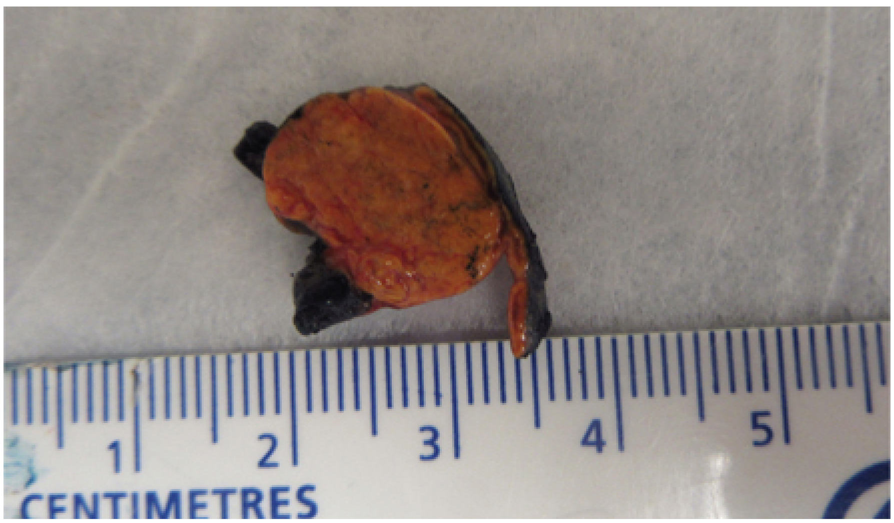

Figure 4-3. Gross photograph of an adrenalectomy specimen with a functioning cortical adenoma, causing Cushing syndrome. The adrenal gland contains a large tumor that has a yellow cut surface that resembles the color and texture of the normal cortex. Note the striking atrophy of the nontumorous cortex.

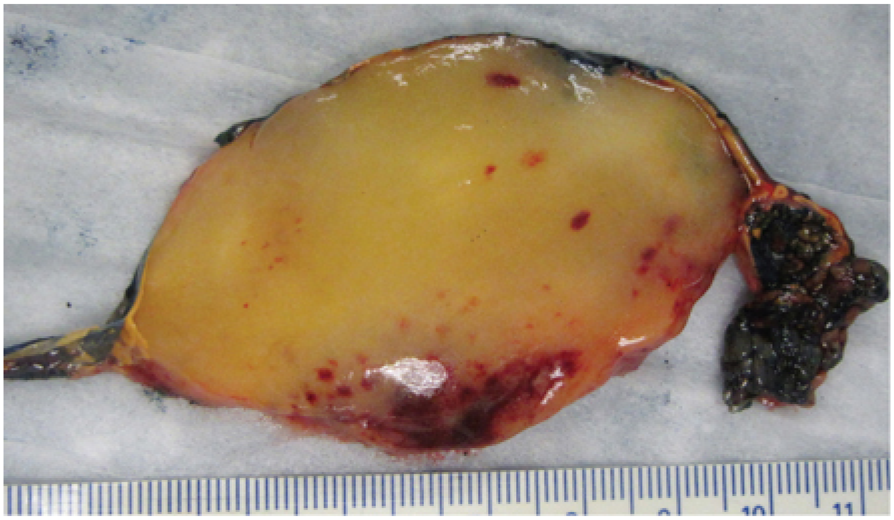

Figure 4-4. Gross photographs of an adrenalectomy specimen with a myelolipoma. The adrenal gland contains a large tumor that has a bright yellow, fatty cut surface. The nontumorous cortex is attenuated around the lesion.

The size, delineation and encapsulation, texture, and color of nodules must be appreciated. Myelolipomas have a distinctive fatty appearance (Figure 4-4). Cortical adenomas are usually yellow; those associated with Conn syndrome are generally bright golden yellow (Figure 4-5), whereas those associated with Cushing syndrome have dusky areas and the characteristic atrophy of the nontumorous cortex (Figure 4-3); exceptional examples can be black.[1] Pheochromocytomas are dusky brown (Figure 4-6) and may be cystic or hemorrhagic, but those in patients with von Hippel Lindau syndrome can have lipid degeneration that gives them a yellow appearance, resembling a cortical adenoma (Figure 4-7).[4] Ganglioneuromas can have a fibrous appearance (Figure 4-8). Carcinomas are large, usually weighing more than 100 g, and have mottled cut surfaces with areas of hemorrhage, cystic degeneration, and necrosis (Figure 4-9).

Figure 4-5. Gross photograph of an adrenalectomy specimen with a functioning cortical adenoma, causing Conn syndrome. The adrenal gland contains a tumor that has a bright yellow cut surface. Note that the surrounding and adjacent adrenal gland appears grossly normal.

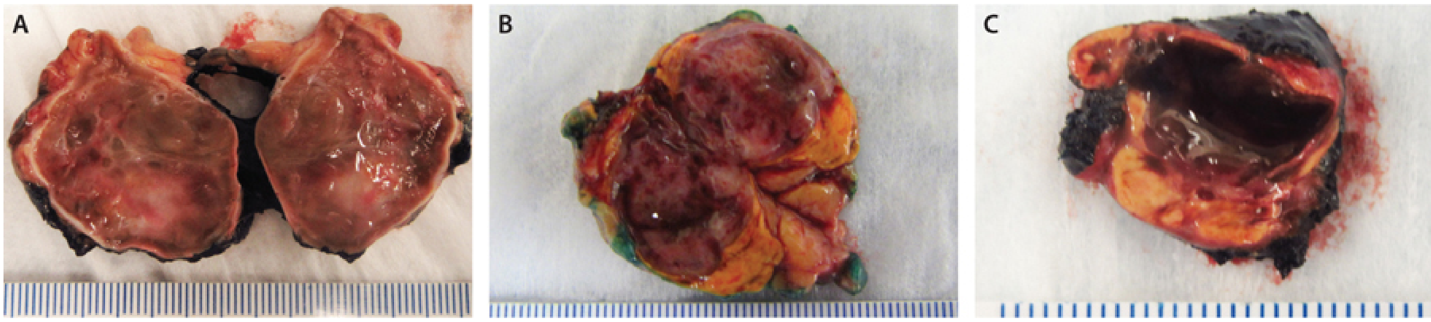

Figure 4-6. Gross photographs of pheochromocytomas. A-C. The adrenal glands contain tumors that are dusky in color and have variable degrees of cystic change. Note that the surrounding and adjacent adrenal gland appears grossly normal.

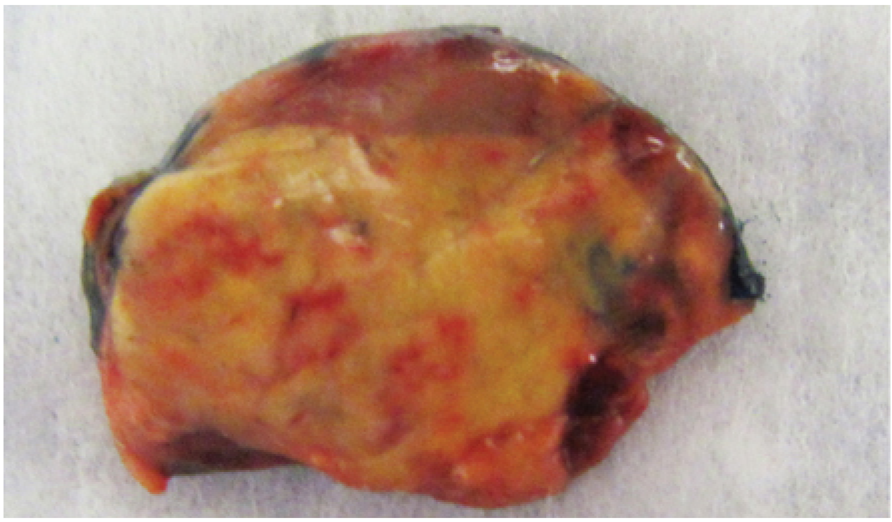

Figure 4-7. Gross photograph of a pheochromocytoma from a patient with von Hippel Lindau disease. The adrenal gland contains a tumor that appears to be yellow, resembling a cortical lesion; however, this is a pheochromocytoma that was associated with catecholamine excess. The tumor is composed of medullary cells that have lipid cytoplasm, and there is lipid degeneration of the stroma.

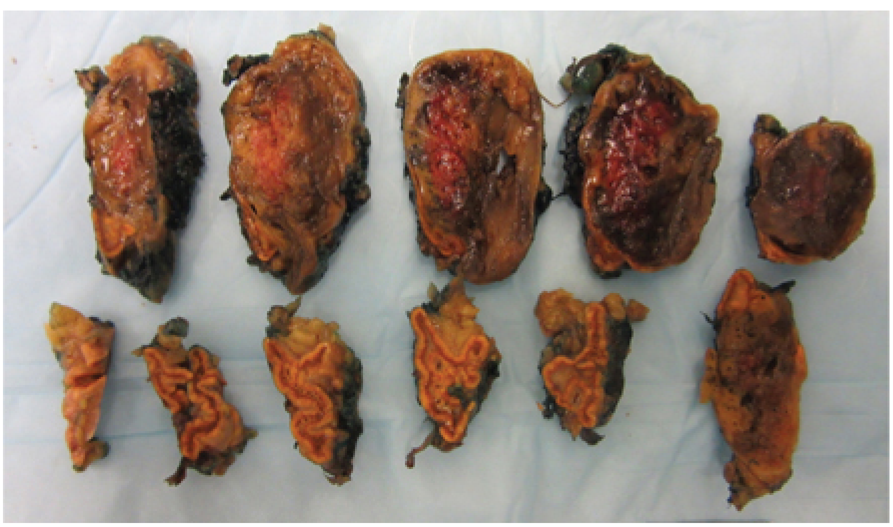

Figure 4-8. Gross photograph of a composite pheochromocytoma/ganglioneuroma. The specimen is shown after sectioning; note the sections of nontumorous gland as well as the lesion. The tumor has areas of red and dusky tumor consisting of pheochromocytoma as well as shiny grey areas that correspond to areas of predominant ganglioneuroma components.

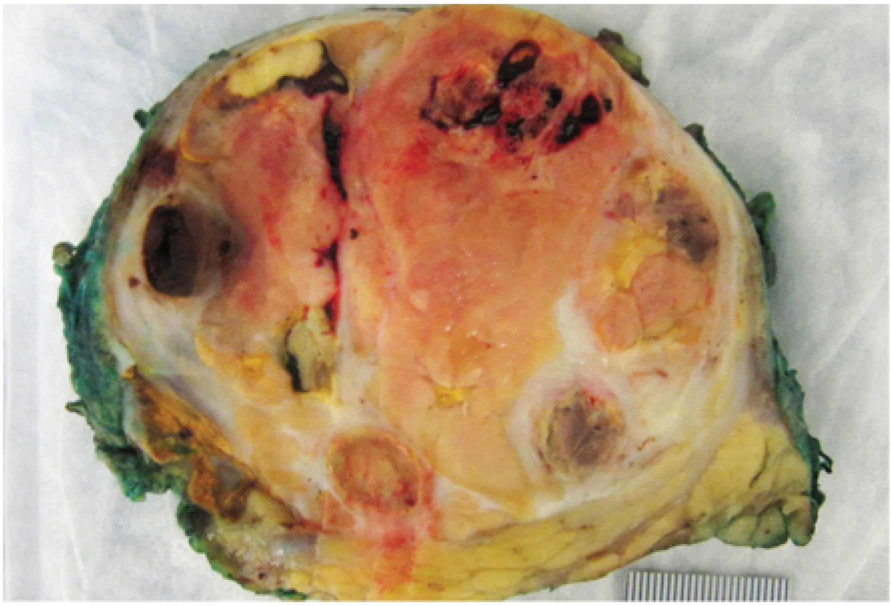

Figure 4-9. Gross photograph of an adrenal cortical carcinoma. This adrenalectomy specimen contains a large tumor with areas of fibrosis, hemorrhage, and cystic degeneration. Note the attenuated adrenal cortex at the top left around the lesion and the normal gland at the bottom left.

Correlation with the microscopic findings will dramatically enhance diagnostic accuracy.

IV. Dissection technique: step-by-step description

1. How to orient adrenal resection specimens

The normal adrenal has two wings and a tail as shown in Figure 4-1; the gland can be easy to orient if not distorted. The presence of a large lesion usually distorts the gland that is attenuated around the nodule. Orientation of a large distorted gland can only be performed if the surgeon provides sutures to indicate landmarks.

If the specimen is a laparoscopic adrenalectomy specimen that required morcellation during removal (Figure 4-10), the specimen cannot be oriented.

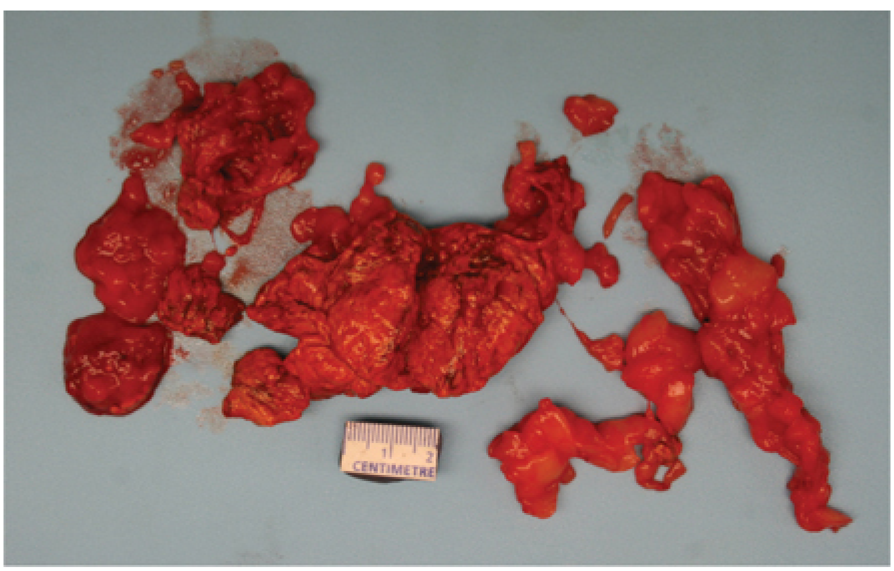

Figure 4-10. Gross photographs of a morcellated adrenalectomy specimen. The adrenal gland is morcellated, and the specimen consists of multiple small and large pieces of adrenal gland with tumor and nontumorous admixed.

2. Resection margin documentation

An intact adrenalectomy specimen should be painted for margin documentation and analysis. Ink the outer surface of the specimen, apply acetone/acetic acid to fix the ink, then pat and air dry.

3. Measurements

The adrenal should be measured to provide three dimensions. The specimen should be weighed. If there is adherent fat, which is usually the case, the specimen should be weighed initially with the adherent tissue, then the adherent fat should be carefully removed and the gland weighed alone.

If the specimen is morcellated, the number of pieces should be described, the aggregate dimensions provided, and the specimen must be weighed.

4. External examination

The external surface of the gland may have adhesions. Any surface nodules should be identified, described and measured; these may be lymph nodes or paraganglia.

5. Sectioning

The gland should be sectioned every 2 to 3 mm (Figure 4-8). This allows careful examination of the entire parenchyma to identify the lesion and the nontumorous gland.

If a tumor or multiple tumors are identified, each should be measured and described, including (a) location; (b) the presence and thickness of a capsule and the nature of the periphery of the lesion (well delineated vs infiltrative); (c) the texture of the lesion (soft vs firm or hard, calcification, if any); (d) the color of the lesion's cut surface; (e) cystic change or hemorrhage, if present; and (f) quantity and appearance of cyst contents and quality of cyst lining.

6. Tissue banking

If tumor is grossly present and a research protocol is available, tissue banking should be considered, following institutional guidelines. Tissue banking for future studies—such as molecular, flow cytometry, next-generation sequencing, and other potential research projects—should be considered. Document the "cold ischemia time," if appropriate (varies by institution), and the type of medium used, if any. Collect fresh tissue or snap-frozen tissue for special studies, according to protocol. Formalin-fixed paraffin-embedded tissue that is representative of biobanked tissue assists in confirmation of material studied and, when required, can be repatriated to diagnostic tissue, as occasionally may be necessary for small lesions.

7. Fixation

Fix the specimen for several hours or overnight, depending on workload and scheduling. Ideally, paper towel should be placed between sections to ensure that they remain flat, and the lobe should be wrapped in paper towel to ensure integrity of the anatomy. Even after a few hours' fixation, it will be much easier to provide well-fixed sections, and the subsequent microscopic staging will probably be much more accurate.

8. Submitting sections

In most cases, the entire specimen should be submitted in serial sections, which allows more accurate examination of large lesions, permits documentation of incidental findings, and allows analysis of the nontumorous gland. The adherent fat should be examined, and any nodules that may be lymph nodes or other important structures should be submitted for microscopic examination.

If the lesion is large, submission of the entire tumor may not be feasible. In this case, the entire capsule of the lesion(s) should be submitted, along with representative sections of the center of the lesion, to include representative sections of all areas with distinct gross appearances. Multiple sections of the capsule may be submitted in one cassette. The entire painted resection margin of the lesional tissue must be submitted for histologic examination.

The nontumorous adrenal should be sampled as much as possible to determine the presence of additional lesions, including underlying nodules, hyperplasia, inflammation, and other neoplasms.

9. Documentation of sections

Document the gross description, ink code, and section code details as illustrated in section V, below.

V. Gross descriptions using paragraph system

The paragraph system can be used to describe adrenal biopsies and resection specimens.

Biopsy

The specimen identified with the patient's name and as "left adrenal biopsy" consists of a core of soft yellow tissue that measures 0.1 cm in diameter x 0.8 cm in length. The specimen is submitted in toto.

Section code

1A: Submitted in toto

Adrenalectomy

The specimen identified with the patient's name and as "right adrenal" consists of an adrenal gland with adherent fibroadipose tissue; the specimen weighs 40.6 g and measures 6.2 x 4.5 x 3.5 cm. The surface has fibrous adhesions and is painted with ink (see ink code). The adherent fat is removed and the adrenal gland weighs 35.7 g and measures 5.9 x 4.2 x 3.2 cm.

There are 2 nodules that measure 3.8 x 2.9 x 2.5 and 0.6 x 0.5 x 0.5 cm located at opposite ends of the gland. The nodules are well delineated/poorly defined and have a yellow, focally tan, and hemorrhagic cut surface.

The nontumorous adrenal is identified and is attenuated around the nodules.

In the periadrenal fibroadipose tissue there are 2 nodules consistent with lymph nodes that measure 0.3 x 0.2 x 0.2 cm.

Representative sections of nodule and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code

Posterior surface: black

Isthmic resection margin: red

Anterior surface: yellow

Section code

2A-T: Larger nodule in toto

2U,V: Smaller nodule in toto

2W-Y: Nontumorous adrenal

2Z: Nodule(s) identified in periadrenal fat

Morcellated adrenalectomy

The specimen identified with the patient's name and as "right adrenal" consists of multiple pieces of soft tissue that weigh 25.2 g and measure 5.2 x 4.0 x 0.8 cm in aggregate.

Several pieces consist of a lesion that is yellow/dusky/hemorrhagic, while others contain recognizable nontumorous adrenal. Representative sections of nodule and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Section code

3A-J: Representative sections/submitted in toto

3K,L: Nodule(s) in periadrenal fat

VI. Common pathologic findings

Adrenal biopsy

Based on the indications for adrenal biopsy listed above, the following common pathologic findings are often identified:

- Metastatic carcinoma
- Lymphoma or leukemia
- Infectious process
- Adrenal cortex

Adrenalectomy

Based on the indications for adrenalectomy listed above, the following common pathologic findings are often identified:

- Cortical adenoma or carcinoma
- Pheochromocytoma

- Myelolipoma
- Ganglioneuroma, neuroblastoma, or composite medullary lesion
- Cyst or pseudocyst
- Inflammatory or infiltrative lesion

Bilateral adrenalectomy

Based on the indications for bilateral adrenalectomy listed above, the following pathologic findings are usually identified:

- Secondary cortical hyperplasia
- Primary pigmented adrenocortical disease (PPNAD)
- Macronodular adrenocortical hyperplasia

VII. Common potential pitfalls and solutions

Adrenal tissue is difficult to cut because of the abundance of lipid. Calcified lesions may require decalcification. These problems result in cracked, folded or torn sections, sections that are missing parts of nodules, and incomplete sections that may be missing the painted resection margin. It is important for the histotechnologists to be aware of these problems to ensure the highest quality sections.

As with any other tissue, cross-contamination can be a problem. The bench must be cleaned before a new case is examined, and all instruments must be clean.

Orientation of the lesion can be problematic in complex specimens. If in doubt, the surgeon should be consulted to help with specimen orientation.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

A synoptic approach to reporting thyroid cancer specimens has been provided by the College of American Pathologists,[5] and a synoptic report has been proposed for adrenal medullary lesions as well.[6] The details of this synoptic report should all be completed and must include the following:

- The main pathology identified, usually the nature of the nodule or cyst or the type of inflammatory lesion; include all relevant classification of morphologic variant, architecture and cytologic classifications, and so forth
- The nature of the nontumorous adrenal, any evidence of atrophy or hyperplasia
- The size and stage of the lesion
- Information about lymphatic invasion, angioinvasion, and perineural invasion
- If multiple lesions are present, identify the secondary and other pathologies
- Number of lymph nodes involved with metastatic malignancy; how many lymph nodes were examined, and how many harbor a metastasis
- Information about other tissues included in the specimen
- The procedure that was performed and structures/ organs present

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5. Thyroid

Sylvia L. Asa, MD, PhD

Thyroid resection specimens include lobectomy, hemithyroidectomy (lobe plus isthmus), subtotal thyroidectomy (lobe, isthmus, and partial contralateral lobe), and total thyroidectomy. The term *subtotal thyroidectomy* is often misused, and hemithyroidectomies are sometimes erroneously classified in this category. The true subtotal thyroidectomy procedure—that is, removal of a complete lobe and isthmus and most of the contralateral lobe while sparing the posterior surface of that second lobe to preserve parathyroids—is now rarely performed because improved microdissection techniques allow better identification of parathyroid glands. Rarely, only the isthmus is resected, constituting an isthmusectomy specimen. Thyroglossal duct cysts are removed by the Sistrunk procedure. Thyroidectomies may include dissections of soft tissue from various parts of the neck. The grossing of neck dissection specimens is covered elsewhere.

Pathologic examination is the gold standard for carcinoma staging, which offers critical information for the prognosis, therapeutic choices, and future care of the patient. Thyroidectomy may constitute the therapy for medical conditions. Appropriate handling of the specimen is the first step and serves as the foundation for the diagnostic and staging process. The pathology report is not only a medical but also a legal document for future therapeutic protocols. Pitfalls exist when difficult settings are encountered. We will discuss in detail appropriate specimen handling, microscopic evaluation, and the pertinent information to include in the pathology report.

I. Indications for thyroid resections

Thyroid *lobectomy* (Figure 5-1A), *hemithyroidectomy* (Figure 5-1B), or *isthmusectomy* (Figure 5-1C) is used to remove thyroid nodules that are at low risk of metastasis clinically and on fine-needle aspiration biopsy (FNAB), or for diagnostic purposes when a lesion is not diagnosed clinically and on FNAB. Lobectomy and isthmusectomy are procedures used for resection of small lesions that can be easily removed. Removal of less than a lobe is not usually indicated because of complications of bleeding and interference with the capsule of a lesion that requires careful histologic examination. Hemithyroidectomy is a procedure used for resection of moderate-sized lesions or for most lesions involving the isthmus.[1]

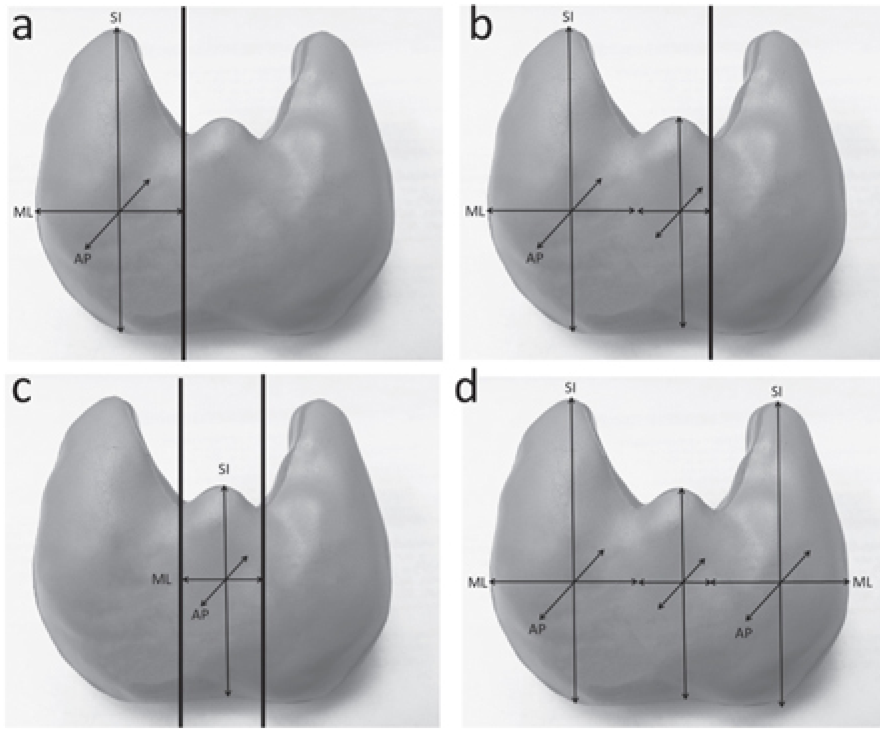


Figure 5-1. Schematic depictions of thyroidectomy specimens, with orientations and measurements. A. Thyroid lobectomy specimen. B. Hemithyroidectomy specimen. C. Isthmusectomy specimen. D. Total thyroidectomy specimen.

Total thyroidectomy (Figure 5-1D) is a procedure used for resection of large and high-risk malignancies or for large thyroid goiters. The handling of a *subtotal thyroidectomy* specimen should follow the same procedures described for total thyroidectomy, with the additional identification of the posterior lobe that was left behind. The *Sistrunk procedure* is specifically designed for the removal of a thyroglossal duct cyst.

II. What do we expect to see in a thyroid resection specimen macroscopically and microscopically?

The findings may include normal, diffusely abnormal, and nodular thyroid tissue. Comprehensive evaluation of the specimen is critical for the assessment of the lesion(s) to establish future possible management plans. The only way to accurately report the actual disease is to have appropriate measurements, weights, and sampling for microscopic assessment.

The size of each component of the specimen is an important feature that must be documented, which includes three dimensions (Figure 5-1). The weight of the specimen is important to document. The number, size, and gross morphology of surface nodules and parenchymal nodules are key elements of the gross description.

The identification of surface lymph nodes is important to determine extent of disease when a nodule is malignant. The superior isthmic region is where the Delphian node is located. This node is so called because of its predictive importance: just as the Oracle of Delphi predicted the future, this node plays an important role as an early site of local spread of thyroid cancers. It is important to identify and examine this node and any others on the thyroid surface, noting their location.

The Sistrunk specimen usually includes soft tissue with a cyst and usually at least a portion of the hyoid bone. Findings may include soft tissue, a cyst, and scant amounts of thyroid tissue. The size of the specimen and the size of the cyst are the two most critical pieces of information and should include three dimensions. The size of the bone is also important to document. The gross morphology of any nodules is key. The cyst should be opened, and both the contents and the lining should be described. It is critical to identify any papillary structures and calcifications in the cyst wall.

The surgeon may biopsy one or more parathyroid glands to ensure preservation of parathyroid tissue. This will usually involve an intraoperative consultation. The small biopsy will be frozen or, in some institutions,

examined by touch preparation.

If any suspicious or unusual lymph nodes are seen during surgery, they may also be biopsied. The superior isthmic region is where the Delphian node is located. The central compartment may be resected with the specimen; this is usually ipsilateral only in lobectomy or hemithyroidectomy specimens and may include the entire bilateral central compartment with total thyroidectomy. In cases of cancer where lateral node involvement is documented or suspected, there may be lateral neck dissection specimens that are received. These are covered elsewhere.

Occasionally, these procedures may also resect portions of adjacent tissues, such as tracheal rings or small portions of esophagus that may be involved with tumor. Rarely, a total laryngectomy is required to excise a large and invasive thyroid tumor.[2]

III. Typical gross photos of thyroid resection specimens

Gross diagnosis based on macroscopic observation is critical, particularly in noting areas with different appearances and submitting them for microscopic examination. The size, delineation and encapsulation, texture, and color of nodules must be appreciated; the presence of colloid translucence and cysts with smooth, granular, or papillary lining should be noted. Correlation with the microscopic findings will dramatically enhance diagnostic accuracy.

Gross photographs of thyroid specimens are presented as follows: a thyroid lobectomy specimen in Figure 5-2, hemithyroidectomy specimens in Figure 5-3, various total thyroidectomy specimens in Figure 5-4, a total thyroidectomy with a total laryngectomy specimen in Figure 5-5, and a thyroidectomy with a Sistrunk resection in Figure 5-6.

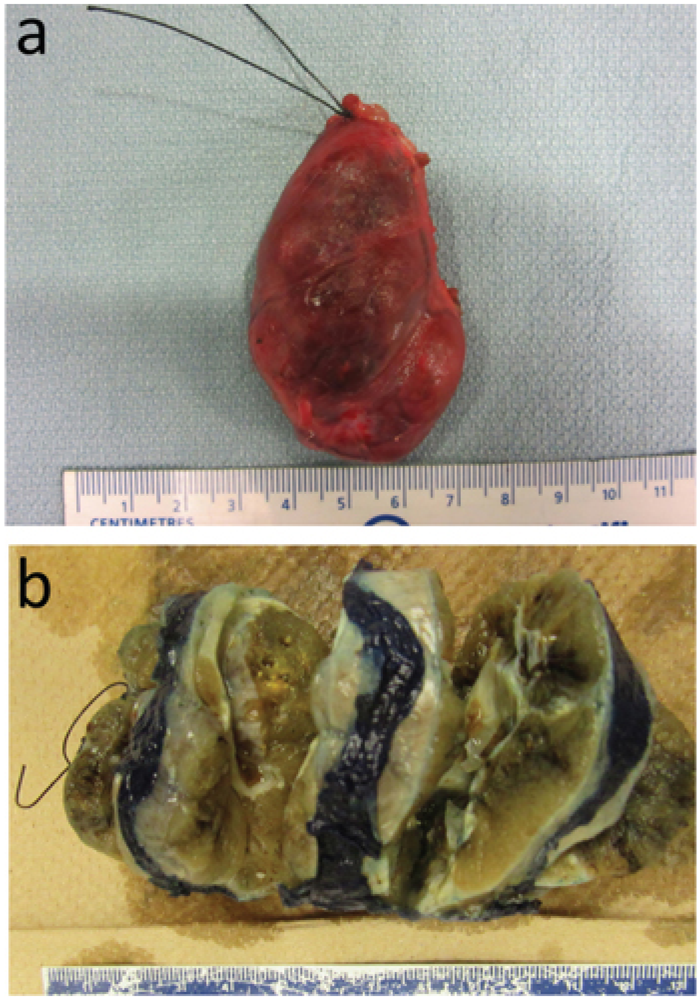


Figure 5-2. Gross photograph of a thyroid lobectomy specimen. A fresh thyroid lobectomy specimen (A) and (B) a thyroid lobe with a large nodule replacing most of the lobe after sectioning and fixation. Note the nodule's capsule and focal calcification.

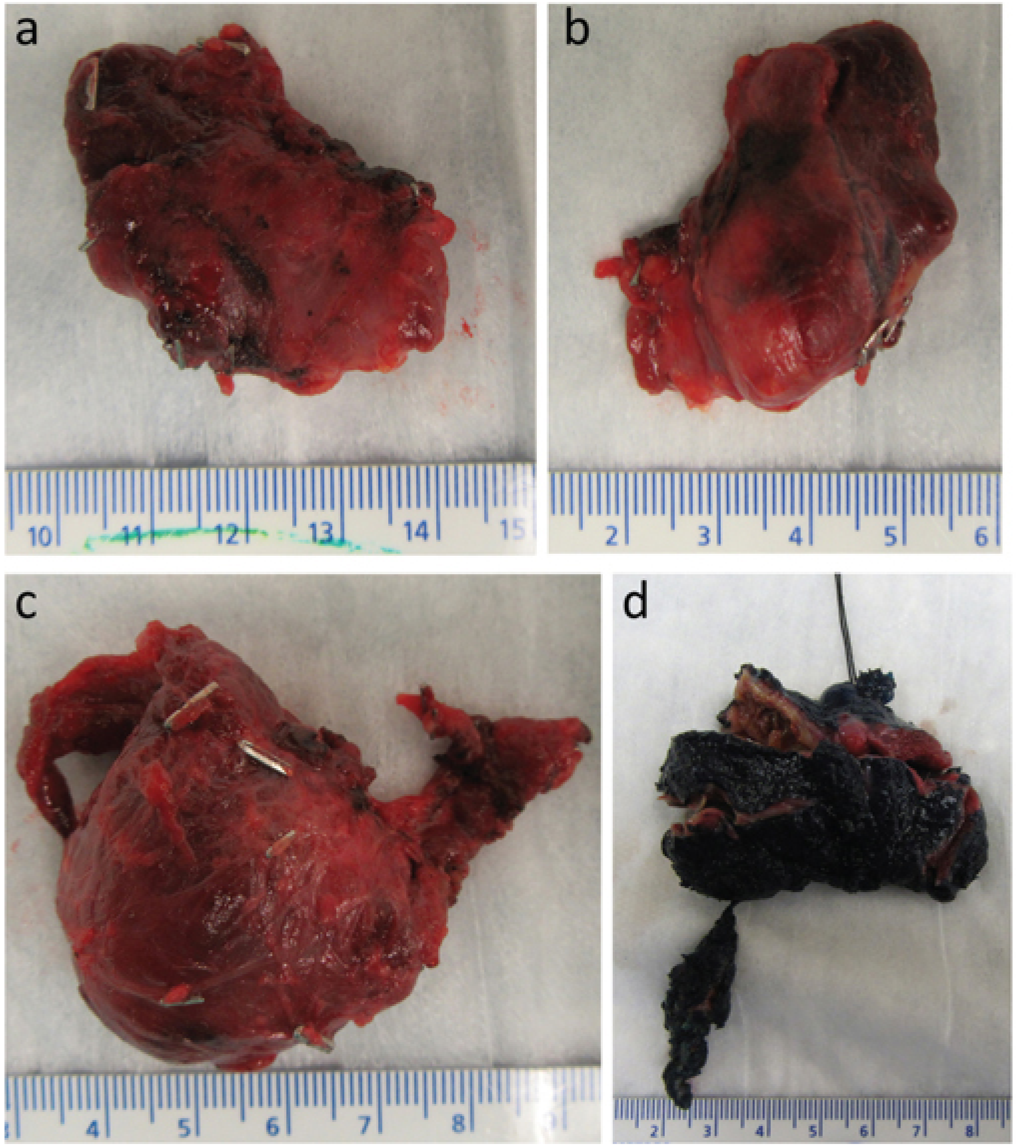


Figure 5-3. Gross photographs of hemithyroidectomy specimens. A, B. Left hemithyroidectomy specimen, anterior view in (A) and posterior view in (B). C. Hemithyroidectomy with large nodule in lobe. D. Hemithyroidectomy with portion of central compartment. Note that figure part D is significantly reduced in size compared to those in parts A through C.

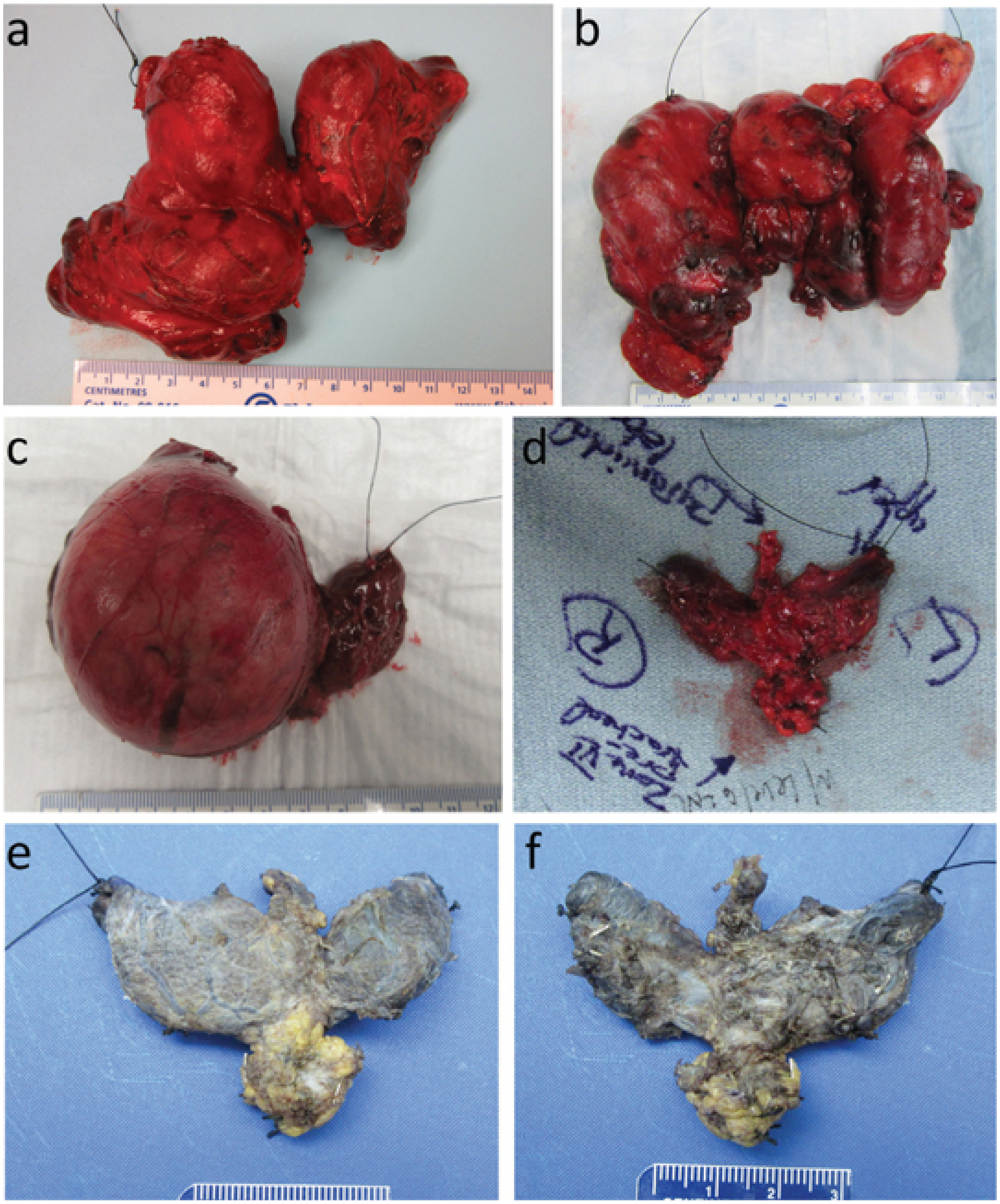


Figure 5-4. Gross photographs of total thyroidectomy specimens. (a) Total thyroidectomy with right nodule and right central compartment (suture marking right upper lobe). (b) Multinodular goiter (short suture left upper lobe, long suture right upper lobe). (c) Total thyroidectomy with large right nodule (suture marking left upper lobe). (d) Total thyroidectomy with central compartment (level 6 neck) dissection. Note prominent pyramidal lobe.

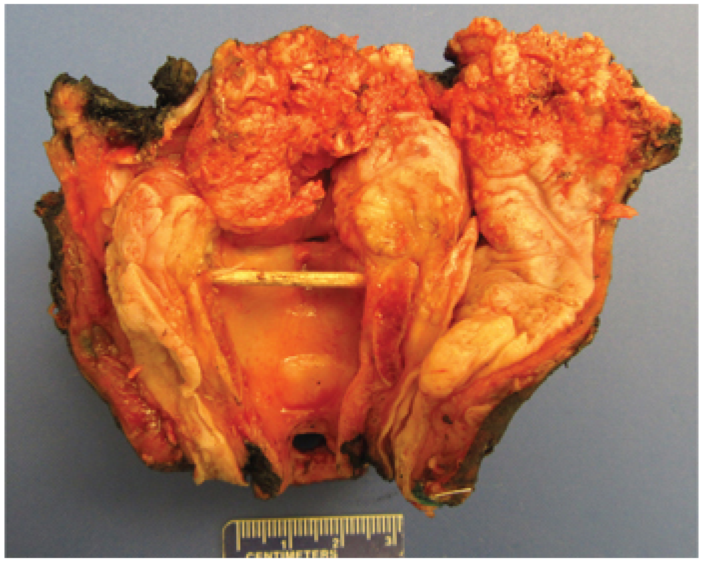


Figure 5-5. Total thyroidectomy with total laryngopharyngectomy specimen.

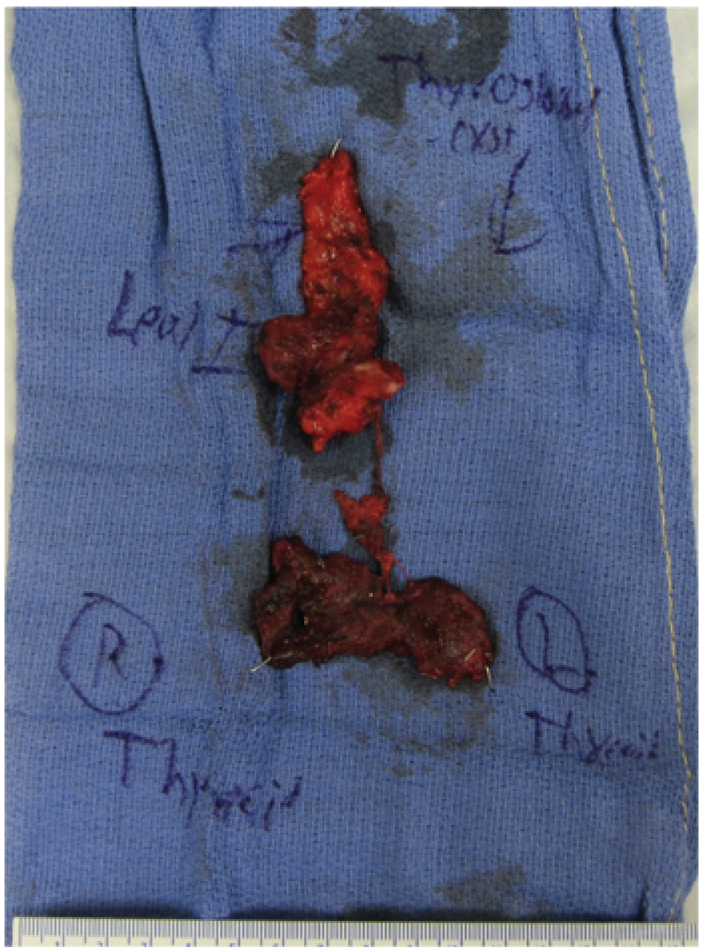


Figure 5-6. Gross photograph of a thyroidectomy with a Sistrunk procedure specimen.

IV. Dissection techniques: step-by-step description

1. How to orient thyroid resection specimens

The thyroid lobe can be easy to orient if not distorted. A normal thyroid lobe is more concave posteriorly, whereas it is convex anteriorly; however, a lobe that is distorted by nodule(s) can be difficult to orient.

The isthmus may be clearly distinct, but in some cases it may merge with the lobe, creating a challenge to measure each component. A photograph is helpful to document the gross appearance and indicate planes used

for sectioning to separate the lobe from the isthmus.

The thyroid isthmus is difficult to orient when removed alone. Many surgeons indicate the superior pole of a lobe or isthmus with a suture to ensure accurate orientation.

The Sistrunk procedure specimen is composed of soft tissue and bone; the site of attachment to the hyoid bone and location of any lesions are the key elements to describe. Usually the surgeon will indicate the orientation with a suture.

2. Resection margin documentation

Ink the outer surface of the specimen. Apply acetone/acetic acid to fix the ink, then pat and air dry.

3. Measurements

As shown in Figure 5-1, the lobe(s) should be measured to provide the supero-inferior (SI), mediolateral (ML), and anteroposterior (AP) dimensions. The isthmus should be measured to provide the SI, ML, and AP dimensions.[3] The specimen should be weighed. If there is an adherent neck dissection component, the specimen should be weighed initially with the adherent tissue. The dissection should then be removed and the lobe weighed alone.

The Sistrunk procedure specimen should be measured to provide the SI, ML, and AP dimensions. The specimen should be weighed. The bone should be measured.

4. External examination

The external surface of the gland may have adhesions. Any surface nodules should be identified, described, and measured; these may be lymph nodes, parathyroid glands, or thyroid nodules that can be attached to the main body of the gland by fibrous tissue. It is important to note that the thyroid gland does not have an anatomic capsule; although there are fascial planes that demarcate this gland, satellite nodules of thyroid tissue are found in perithyroidal fat and may be particularly prominent in pathological situations, including thyroiditis and follicular nodular disease. These foci may also be the site of neoplastic transformation, giving rise to primary tumors outside the usual boundaries of the gland.

It is particularly important to note that the thyroid gland does not have an anatomic capsule, and, in the isthmus, the gland is admixed with skeletal muscle.[4]

5. Sectioning

The thyroid lobe should be sectioned in the transverse plane, with sections every 2 to 3 mm (Figure 5-7A). This allows careful examination of the entire lobe's parenchyma to identify all nodules. In some instances, the upper and lower poles are sectioned in the SI plane to ensure inclusion of the margins (Figure 5-7B).

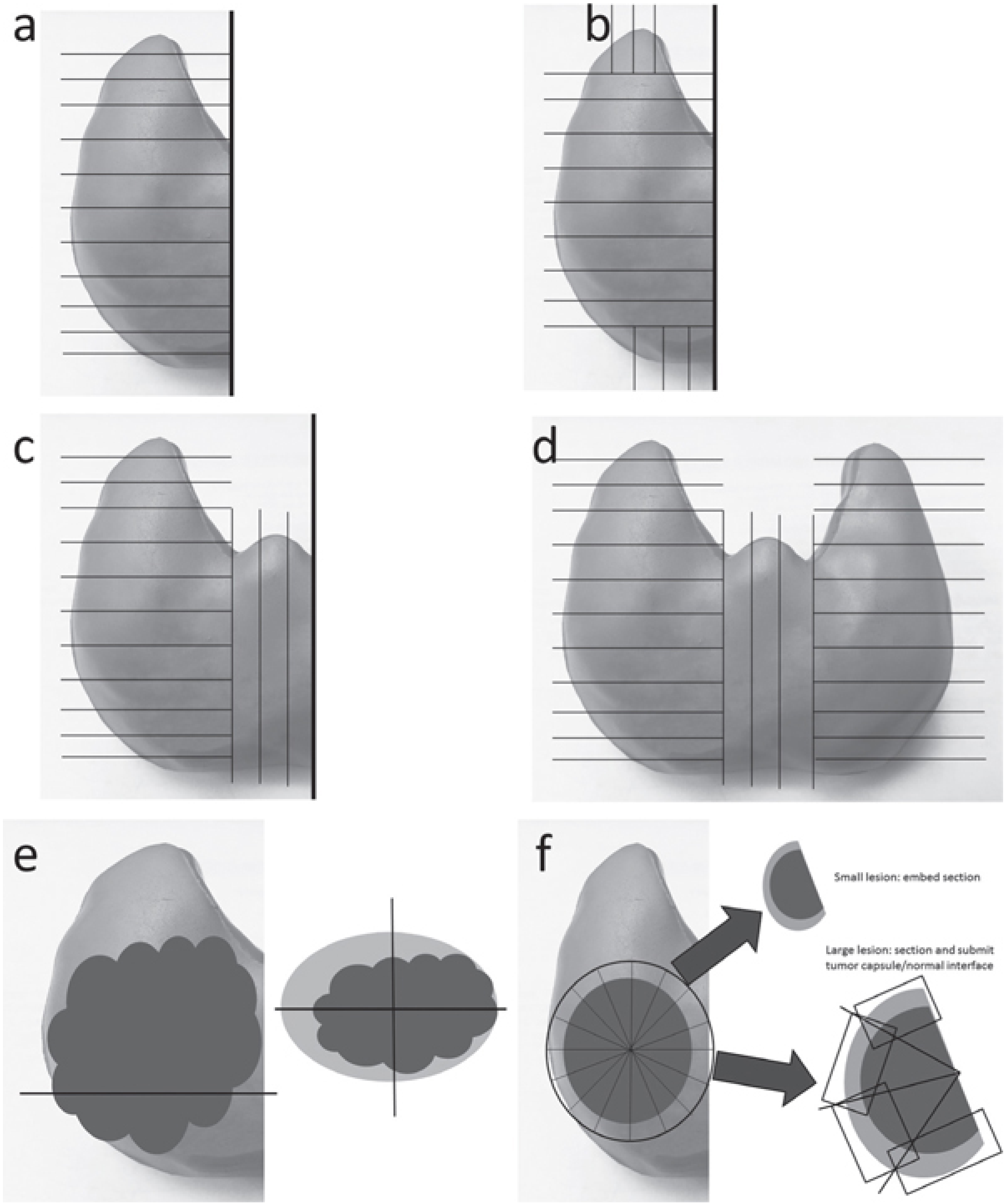


Figure 5-7. Schematic depictions: how to section thyroidectomy specimens. A, B. Schematic depiction of how to section a thyroid lobectomy specimen. C. Hemithyroidectomy specimen. D. Total thyroidectomy specimen. The approach to sectioning and submitting sections of a large nodule are illustrated in (E) and (F). In (E), the nodule is sectioned serially in the horizontal plane, and each horizontal section can be cut into multiple pieces that will each fit into a single cassette. In (F), the "orange skin" approach is illustrated. The lesion can be cut into segments like segments of an orange. Each segment can be embedded if the lesion is small; if the lesion is large, multiple pieces of the capsule can be embedded in a single block, and representative sections of the central part can be examined.

For a hemithyroidectomy or total thyroidectomy, the lobe(s) should be separated from the isthmus at the junction of these two anatomical regions (Figures 5-7C,D). The lobe should be sectioned in the transverse plane with sections every 2 to 3 mm. The isthmus should be sectioned in the SI plane with sections every 2 to 3 mm. This allows careful examination of the entire parenchyma to identify all nodules. As with lobectomy specimens,

the upper and lower poles of the lobes may be sectioned in the SI plane to ensure inclusion of the margins (Figure 5-7B).

Sectioning of the thyroid isthmus when removed in isolation depends on the lesion and its margins. The specimen can be sectioned in either the transverse or the SI sagittal plane, with sections every 2 to 3 mm; the choice depends on the location of nodule(s) and their proximity to margins, and should be determined to ensure the best visualization of the lesion's resection margins. Any nodules identified must also be submitted. In general, these specimens should be submitted in toto.

If a tumor or multiple tumors are identified, each should be measured and described, including (a) location; (b) the presence and thickness of a capsule and the nature of the periphery of the lesion (well delineated vs infiltrative); (c) the texture of the lesion (soft vs firm or hard, calcification, if any);(d) the color of the lesion's cut surface and whether it has colloid translucence; (e) cystic change or hemorrhage, if present; and (f) quantity and appearance of cyst contents and quality of cyst lining.

6. Tissue banking

If tumor is grossly present and a research protocol is available, tissue banking should be considered according to institutional guidelines. Tissue banking for future studies—such as molecular, flow cytometry, next-generation sequencing, and other potential research projects—should be considered. Document the "cold ischemia time," if appropriate (varies by institution), and the type of medium used, if any. Collect fresh tissue or snap-frozen tissue for special studies according to protocol. Formalin-fixed paraffin-embedded tissue that is representative of biobanked tissue assists in confirmation of material studied and, when required, can be repatriated to diagnostic tissue, as occasionally may be necessary for small lesions.

7. Fixation

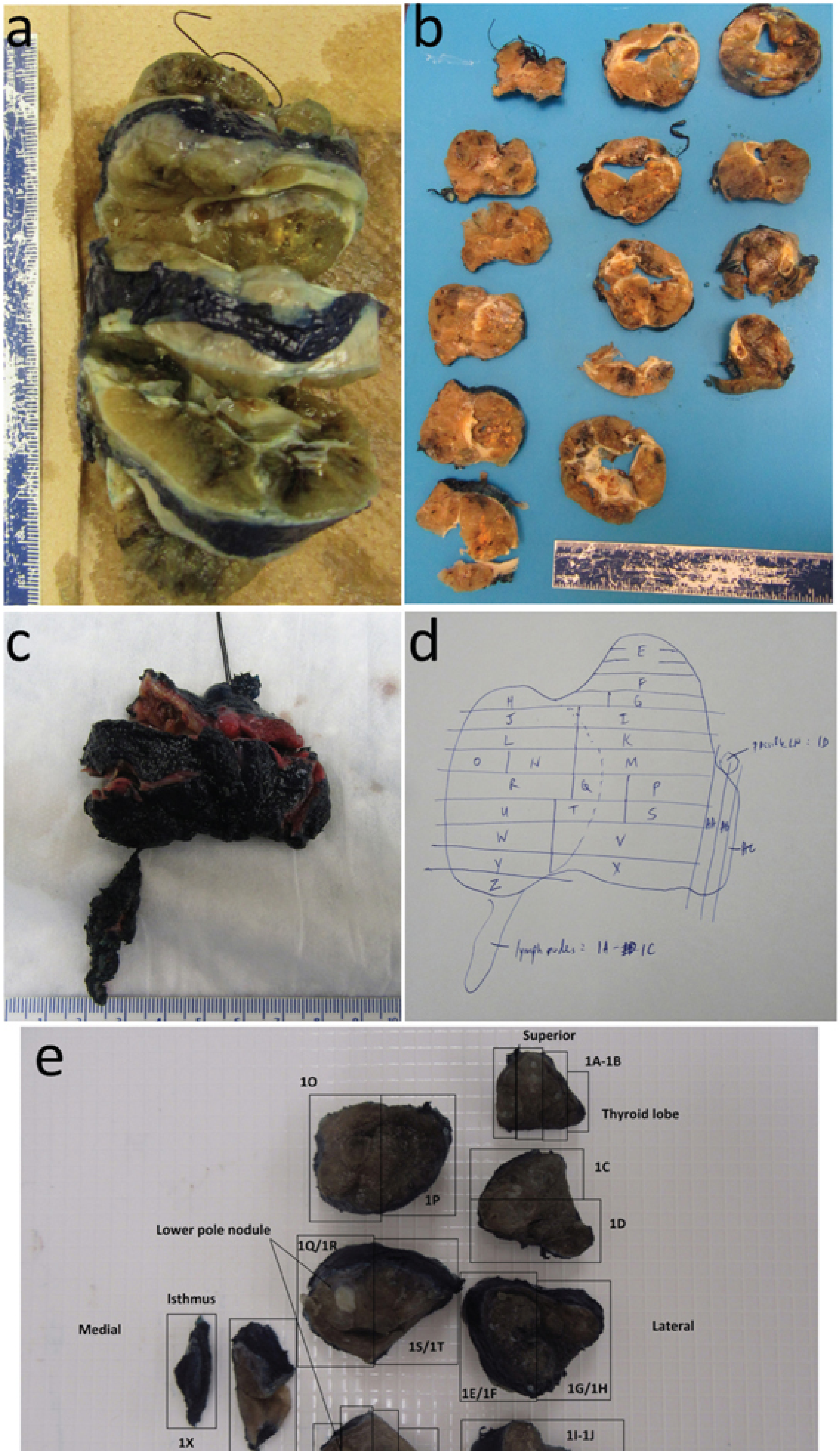
Fix the specimen for several hours or overnight, depending on workload and scheduling. Ideally, paper towel should be placed between sections to ensure that they remain flat, and the lobe should be wrapped in paper towel to ensure integrity of the anatomy. Even after a few hours' fixation, it will be much easier to provide well-fixed sections, and the subsequent microscopic staging will probably be much more accurate.

8. Submitting sections

In most cases, the entire specimen should be submitted in serial sections, lobes superior to inferior, and, for a hemithyroidectomy, the isthmus from the site of attachment to the lobe to the opposite side, which represents the resection margin. In the case of a total thyroidectomy, sectioning of the isthmus should occur from one side to the other, specified in the sections. This allows more accurate examination of grossly identified nodules, also permits documentation of incidental small lesions, and, of importance, ensures documentation and examination of lymph nodes and parathyroids that may not be seen grossly.

If a lesion is large, submission of the entire lobe may entail multiple sections of each slice, as shown in Figure 5-7E. If this is not feasible, the entire capsule of the lesion(s) should be submitted, along with representative sections of the center of the entire lesion, to include representative sections of all areas with distinct gross appearances. When submitting the capsule of a large lesion, the "orange skin" approach (Figure 5-7F) should be used. Multiple sections of the capsule may be submitted in one cassette. The entire painted resection margin of the lesional tissue must also be submitted for histologic examination.

The nontumorous thyroid should be sampled as much as possible to determine the presence of additional lesions, including underlying follicular nodular disease, thyroiditis, and other neoplasms, as well as parathyroids and lymph nodes. If the gland is very large with multinodular disease, this may represent a challenge. In this case, careful documentation of sections and marks to identify the unsampled tissue will facilitate a return to the specimen for further sampling of any nodule(s) that are found to be malignant.


a
b
c
d
e
Superior
1A-1B
Thyroid lobe
1O
1C
1P
1D
Lower pole nodule
1Q/1R
Isthmus
Medial
Lateral
1S/1T
1E/1F
1G/1H
1X
1I-1J

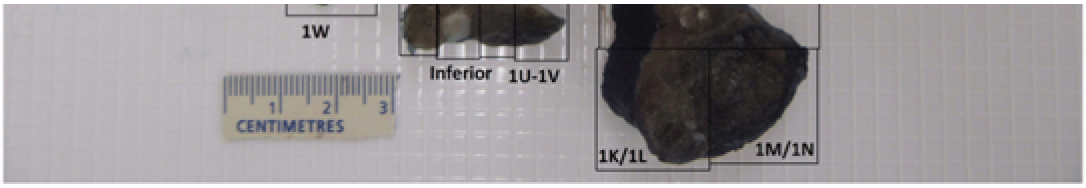


Figure 5-8. Gross photographs of hemithyroidectomy specimens. A, B. The specimen illustrated in Figure 5-2 is shown after sectioning for fixation (A) and after the sections are fixed, separated, and laid out on the dissection bench. C-E. A hemithyroidectomy specimen with portion of central compartment as shown in Figure 5-4D is sectioned according to the annotations (D), and a photograph documents each block submitted (E).

In the case of a large goiter, it is impractical to submit the entire thyroid. In this case, careful documentation of sections and marks to identify the unsampled tissue will facilitate a return to the specimen for further sampling of any nodule(s) that are found to be malignant.

In most cases of isthmusectomy, the entire thyroid isthmus should be submitted in serial sections, either superior to inferior or in the sagittal plane. This allows more accurate examination of grossly identified nodules, also permits documentation of incidental small lesions and, of importance, ensures documentation and examination of lymph nodes and parathyroids that may not be seen grossly.

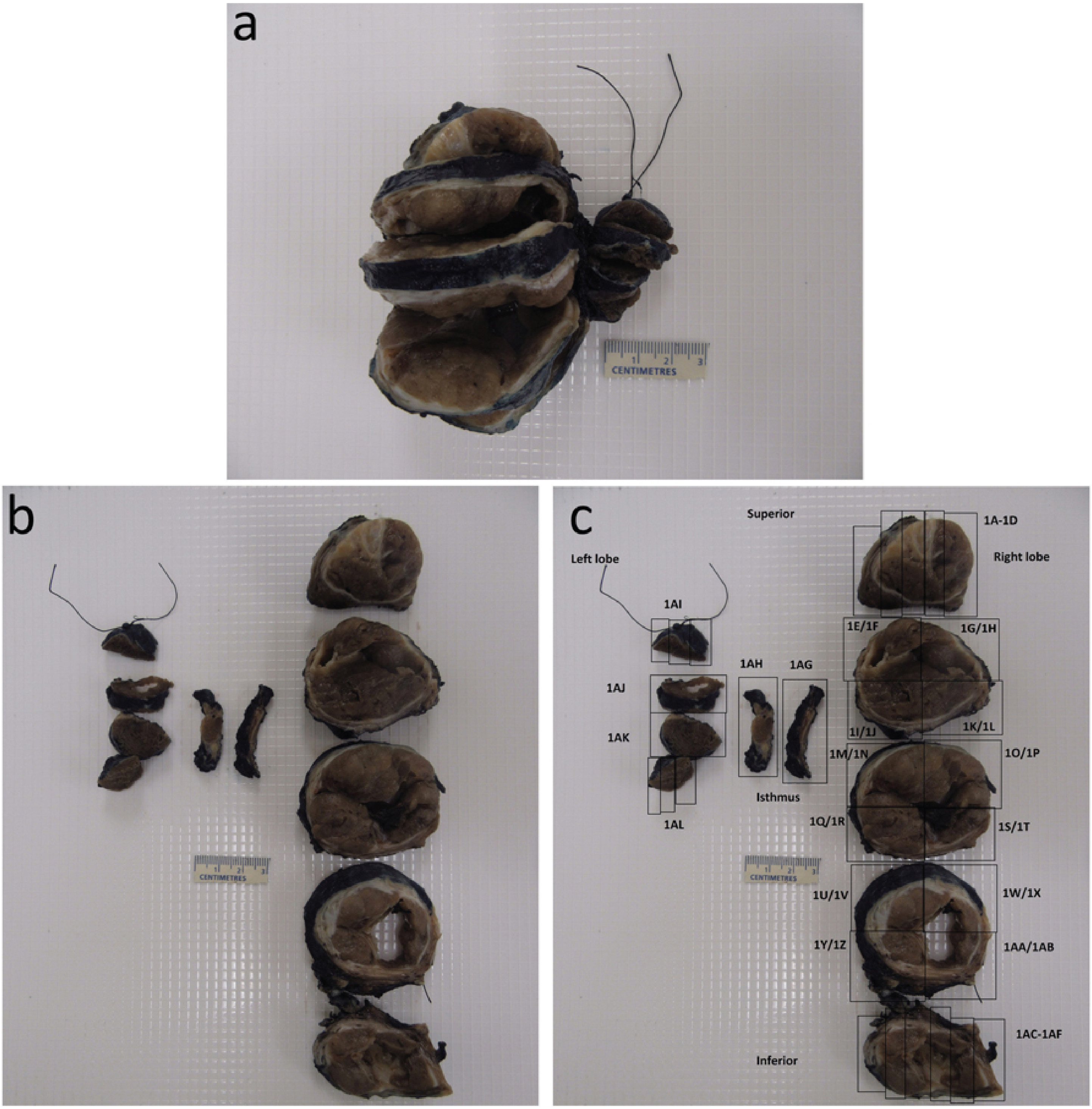


Figure 5-9. Gross photographs of total thyroidectomy specimens. A total thyroidectomy oriented with a suture at the top of the left lobe (A) is sectioned (B) and annotated (C), with a photograph documenting each block submitted.

In most cases, the entire soft tissue of a Sistrunk resection should be submitted in serial sections.

Sections of any nodules on the surface should be examined histologically; these nodules may be included in the full section of the gland when they are small; but when the nodules are large, they should be sampled and identified as separate lesions.

9. Documentation of sections

Document the gross description, ink code, and section code details as illustrated in section V, below.

V. Gross descriptions using paragraph system

The paragraph system can be used to describe thyroid resection specimens.

Lobectomy

The specimen identified with the patient's name and as "right thyroid lobectomy" consists of a lobe of thyroid that weighs 12.5 g and measures 4.3 x 2.8 x 2.2 cm. The surface has fibrous adhesions and is painted with ink (see ink code).

There are 2 surface nodules that measure 0.2 x 0.2 x 0.1 cm located on the posterior inferior surface. On section, there is a nodule that measures 2.8 x 2.5 x 2.3 cm. The nodule is well delineated and has a variegated tan and hemorrhagic surface.

Representative sections of nodule and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code

Posterior surface: black

Isthmic resection margin: red

Anterior surface: yellow

Section code

1A-J: Lobe in toto, superior to inferior

1K,L: Surface nodule(s)

Hemithyroidectomy

The specimen identified with the patient's name and as "left hemithyroidectomy" consists of a hemithyroidectomy specimen that weighs 12.5 g. The lobe measures 4.3 x 2.8 x 2.2 cm and the isthmus measures 2.5 x 0.5 x 0.5 cm. The surface has fibrous adhesions and is painted with ink (see ink code).

There is one surface nodule that measures 0.2 x 0.2 x 0.1 cm located on the lateral inferior surface of the lower lobe. On section, there is one nodule that measures 3.1 x 2.8 x 2.5 cm. The nodule located in the 3.1 x 2.8 x 2.5 is well delineated/poorly defined and have a red-tan colloid-rich cut surface.

Representative sections of nodule and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code

Posterior surface: black

Isthmic resection margin: red

Anterior surface: yellow

Section code

1A-L: Lobe in toto, superior to inferior

1M-O: Isthmus, or left to right; O represents the resection margin en face

1P: Surface nodule

Total thyroidectomy

The specimen identified with the patient's name and as "total thyroidectomy" consists of a total thyroidectomy specimen that weighs 89 g. The right lobe measures 7.0 x 5.0 x 2.7 cm, the left lobe measures 6.0 x 5.0 x 3.5 cm, and the isthmus measures 3.5 x 2.0 x 0.5 cm. The surface has fibrous adhesions and is painted with ink (see ink code).

There are two surface nodules that measure 0.3 x 0.2 x 0.2 and 0.2 x 0.2 x 0.2 cm located on the posterior inferior surfaces of the right and left lobes, respectively. The right upper lobe contains a poorly delineated nodule that measures 2.2 x 1.8 x 1.5 cm and has a firm grey-tan cut surface. The left lower lobe contains a well-delineated nodule that measures 1.4 x 1.2 x 1.0 cm and has a soft red-tan glistening cut surface.

Representative sections of nodules and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code

Posterior surface: black

Isthmic resection margin: red

Anterior surface: yellow

Section code

1A-L: Right lobe in toto, superior to inferior
1M-P: Isthmus, right to left
1Q-BB: Left lobe in toto, superior to inferior
1CC-DD: Surface nodules

Isthmusectomy

The specimen identified with the patient's name and as "thyroid isthmus" consists of a piece of thyroid tissue that weighs 10 g and measures 5.0 x 3.1 x 1.2 cm. The surface has fibrous adhesions and is painted with ink (see ink code).

There are no surface nodules. On section, the nodule measures 1.5 x 1.3 x 1.0 cm. The nodule(s) is/are well delineated/poorly defined and has a uniform tancut surface.

Representative sections of nodule and normal tissue are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code
Posterior surface: black
Right resection margin: red
Left resection margin: green
Anterior surface: yellow

Section code
1A-E: Isthmus in toto, superior to inferior

Sistrunk procedure

The specimen identified with the patient's name and as "? thyroglossal duct cyst" consists of a piece of fibroadipose tissue with an adherent portion of hyoid bone. The specimen weighs 8 g and measures 1.5 x 1.2 x 1.0 cm. The surface has fibrous adhesions and is painted with ink (see ink code). The piece of bone measures 1.0 x 0.3 x 0.2 cm.

Within the fibroadipose tissue there is a cyst that measures 0.6 x 0.6 x 0.5 cm. It contains hemorrhagic/serous fluid and the lining is smooth without papillary excrescences. There is a nodule with focal calcification; it measures 0.5 x 0.5 x 0.5 cm.

Representative sections of nodule are submitted for biobanking with patient consent. The remainder of the specimen is submitted in toto.

Ink code
Posterior surface: black
Right resection margin: red
Left resection margin: green
Anterior surface: yellow

Section code
1A: Cyst in toto
1B,C: Adjacent nodule(s)

If a parathyroid or lymph node is biopsied during the procedure, this specimen should also be documented.

(2) The specimen identified with the patient's name and as "right paratracheal node" consists of a small piece of soft, tan tissue that measures 1.0 x 0.8 x 0.6 cm. It is sectioned and half is frozen for intraoperative consultation.

2A: Frozen tissue resubmitted
2B: Remainder in toto

Frozen section diagnosis should be documented in the appropriate field, along with documentation of to whom and what time it was reported.

If the central compartment is dissected during the procedure, this specimen should also be documented.

(3) The specimen identified with the patient's name and as "central compartment" consists of a piece of fibroadipose tissue that weighs 3 g and measures 1.9 x 1.7 x 0.7 cm. On section, five nodules are identified;

they measure from 0.1 x 0.1 x 0.1 to 0.6 x 0.4 x 0.3 cm.
3A-D: Nodules in toto

VI. Common pathologic findings

Thyroid lobectomy

Based on the indications for thyroid lobectomy listed above, the following common pathologic findings are often identified[5]:

- Thyroiditis
- Follicular nodular disease
- Thyroid adenoma
- Thyroid carcinoma

Hemithyroidectomy

Based on the indications for hemithyroidectomy listed above, the following common pathologic findings are often identified[5]:

- Thyroiditis
- Follicular nodular disease
- Thyroid adenoma
- Thyroid carcinoma

Total thyroidectomy

Based on the indications for total thyroidectomy listed above, the following common pathologic findings are often identified[5]:

- Thyroiditis
- Follicular nodular disease
- Diffuse hyperplasia (Graves disease)
- Thyroid adenoma
- Thyroid carcinoma

Thyroid isthmusectomy

Based on the indications for thyroid isthmusectomy listed above, the following common pathologic findings are often identified[5]:

- Follicular nodular disease
- Thyroid adenoma
- Thyroid carcinoma
- Thyroiditis

Sistrunk procedure specimens

Based on the indications for Sistrunk procedure listed above, the following common pathologic findings are often identified[5]:

- Thyroglossal duct cyst
- Thyroid carcinoma

VII. Common potential pitfalls and solutions

Thyroid tissue is difficult to cut and sections often curl in the cassette. Fatty tissue is difficult to cut. Calcified lesions may require decalcification. These problems result in cracked, folded or torn sections, sections that are missing parts of nodules, and incomplete sections that may be missing the painted resection margin. It is important for the histotechnologists to be aware of these problems to ensure the highest quality sections. It may be necessary to cut many deeper levels to obtain full sections. This may be of particular importance to obtain sections that include the remnants of the thyroglossal duct that are required to validate the diagnosis in a Sistrunk procedure specimen and to examine capsular invasion and resection margin involvement by malignancies.

Occasionally, tissue is displaced during sectioning. The author has seen examples of skeletal muscle artifactually inserted into a thyroid tumor at the time of grossing, when a blunt blade was used to cut the gland. Thyroid requires fresh and sharp blades for sectioning.

As with any other tissue, cross-contamination can be a problem. The bench must be cleaned before a new case is examined, and all instruments must be clean.

Orientation of the lesion can be problematic in complex specimens. If in doubt, the surgeon should be consulted to help with specimen orientation.

Identification of extrathyroidal extension (ETE) is a controversial feature that has been addressed in the 8th edition of the *AJCC Cancer Staging Manual*.[6] Studies showed that many examples of what pathologists called *minimal ETE* did not impact disease outcome; this was not unexpected because the invasion of fat and other local structures was not biologically significant, as pointed out by Mete et al,[4] who pointed out that the thyroid does not have an anatomical capsule and thyroid tissue is frequently identified in perithyroidal fat. The new guidelines require gross tumor extension into strap muscles; the identification of minor extrathyroidal invasion identified only on histologic examination is no longer a variable in determining stage of the primary tumor.[6] This change underlines the importance of careful gross examination of the thyroid cancer resection specimen.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

A synoptic approach to reporting thyroid cancer specimens has been provided by the College of American Pathologists.[3] The details of this synoptic report should all be completed and must include the following:

- The main pathology identified, usually the nature of the nodule or cyst or the type of inflammatory lesion; include all relevant classification of morphologic variant, architecture and cytologic classifications, and so forth
- The location of the lesion
- The size and stage of the lesion
- The growth pattern of the lesion: infiltrative versus encapsulated, widely invasive versus minimally invasive
- Information about lymphatic invasion, angioinvasion, perineural invasion, and extrathyroidal extension
- If multiple lesions are present, identify the secondary and other pathologies
- Number of lymph nodes involved with carcinoma; how many lymph nodes were examined, and how many harbor a metastasis; the size of the largest metastatic focus
- Information about other tissues included in the specimen, for example, parathyroids and thymus
- The procedure that was performed and structures/organs present

References

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6. Parathyroid

Sylvia L. Asa, MD, PhD

Parathyroid resection specimens include biopsies, single-gland resections, resections of a large gland with biopsy of a second gland, or resections of three glands with biopsy of a fourth gland. Some procedures include resection of the central compartment of the neck and thymus that may contain ectopic parathyroid tissue.

Pathologic examination is the gold standard for diagnosis and management of patients with hyperparathyroidism. The outcomes of pathology examination offer critical information for the prognosis, therapeutic choices, and future care of the patient. The importance of intraoperative parathyroid hormone measurement has become more widely recognized in recent years,[1] and this technology has altered the approach to parathyroid surgery and the role of frozen section for intraoperative consultation. Confirmation of a significant drop in the circulating parathyroid hormone level provides strong evidence of resection of the offending lesion, thereby allowing the surgeon to stop the parathyroidectomy procedure, leaving the rest of the neck intact. In the event of a need for repeat surgery, there is no fibrosis that would interfere with the ability to identify remaining parathyroids.

Appropriate handling of the specimen is an important first step and serves as the foundation for the diagnostic process. The pathology report is not only a medical, but also a legal document for future therapeutic protocols. Pitfalls exist when difficult situations are encountered. We will discuss in detail appropriate specimen handling, macroscopic and microscopic evaluation, and the pertinent information to include in the pathology report.

I. Indications for parathyroid resections

Parathyroid biopsy is the most common parathyroid specimen because it is performed during thyroid surgery. The goal of this procedure is usually to confirm that the surgeon has identified a parathyroid gland to spare during thyroidectomy; the goal is to prevent iatrogenic hypoparathyroidism. Parathyroid biopsy is also performed during parathyroidectomy to confirm the identification of nonlesional glands.

Parathyroidectomy is performed to treat hyperparathyroidism.[1] The surgery may involve resection of a single gland when preoperative investigations have identified a culprit lesion. If the surgeon encounters an unusually large, adjacent gland, there may be a biopsy of a second gland, and, rarely, patients may have double adenomas, resulting in removal of two parathyroids.[2,3] Patients who have multiglandular parathyroid disease, either in the setting of secondary or tertiary hyperparathyroidism or those with genetic predisposition to parathyroid proliferative disorders, usually undergo resections of three glands, with biopsy of the fourth most-normal gland, which is implanted in a surgically accessible location (often the forearm) in the event of recurrent disease.

Central compartment neck dissection and thymectomy may be performed during parathyroidectomy because parathyroid tissue can be found within these tissues.

II. What do we expect to see in a parathyroid resection specimen macroscopically and microscopically?

The findings may include normal, diffusely abnormal, and/or nodular parathyroid tissue. Comprehensive evaluation of the specimen is critical for the assessment of the lesion(s) to establish future possible management plans. The only way to accurately report the actual disease is to have appropriate measurements, weights, and sampling for microscopic assessment.

The size of each component of the specimen is an important feature that must be documented; this includes three dimensions and the weight of the specimen. The orientation of the gland is an important aspect of handling a parathyroid (Figure 6-1); identification of the hilum by the localization of vessels allows proper sectioning, because this is the usual location of nontumorous tissue in glands with neoplasia.

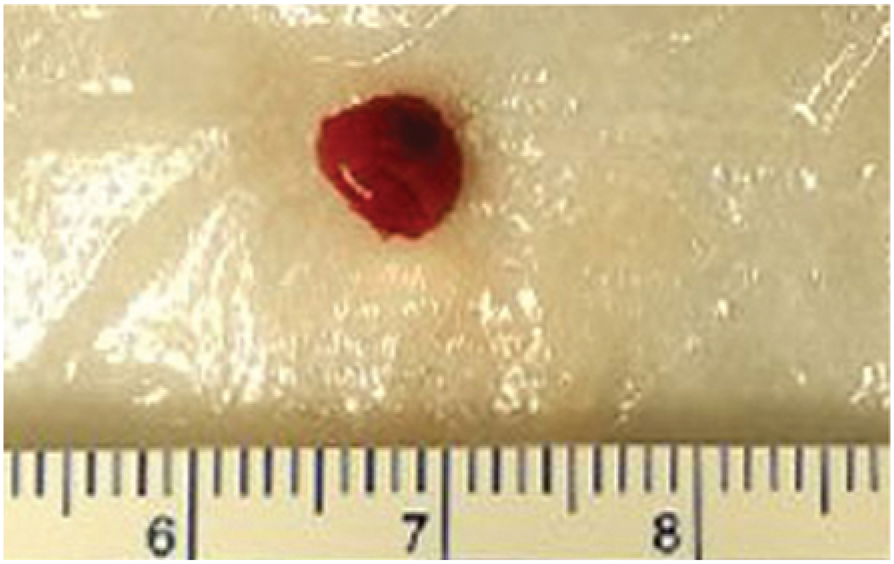

Figure 6-1. Gross photograph of a normal parathyroid gland. Note the hilum at the top right.

Occasionally, these procedures may also resect portions of adjacent tissues, usually central compartment of the neck, thymus, and thyroid. The reader is referred to the chapter on the thyroid for thyroid specimens.

III. Typical gross photos of parathyroid resection specimens

Gross diagnosis based on macroscopic observation is critical, particularly in noting areas with different appearances and submitting them for microscopic examination. The size, delineation and encapsulation, texture, and color of nodules must be appreciated. Correlation with the microscopic findings will dramatically enhance diagnostic accuracy.

Gross photographs of parathyroid glands are provided in Figures 6-2 through 6-4.

Figure 6-2. Gross photograph of a parathyroidectomy specimen. A parathyroid adenoma has a smooth external surface and rich vascularization. Note the normal gland at the left upper edge; sections should include this area for documentation of the normal tissue.

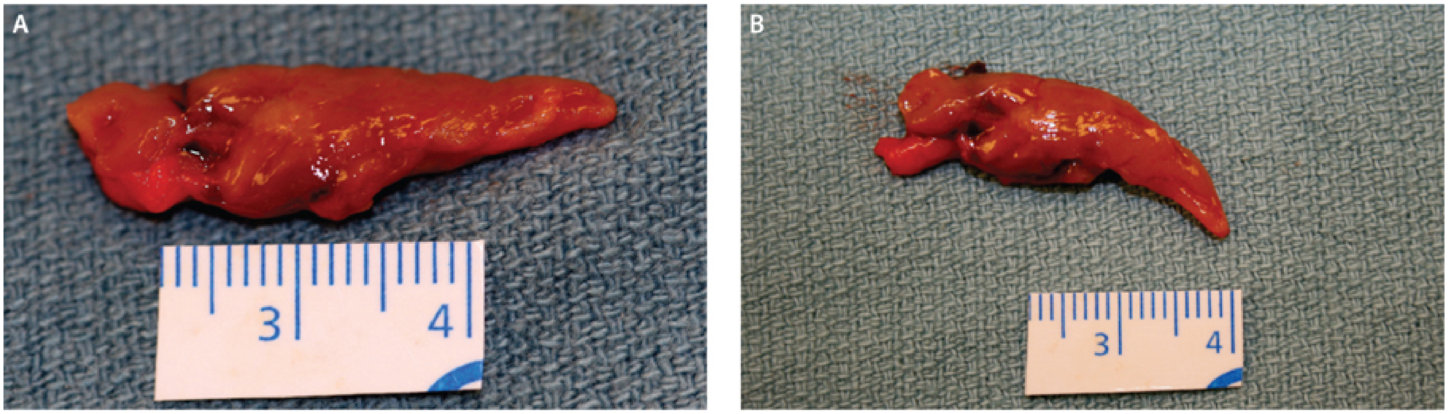

Figure 6-3. Gross photographs of a parathyroidectomy specimen. A parathyroid adenoma has a smooth external surface (A). Examination of both surfaces is required to identify the hilum of the gland (B), where remnants of the normal gland can be found.

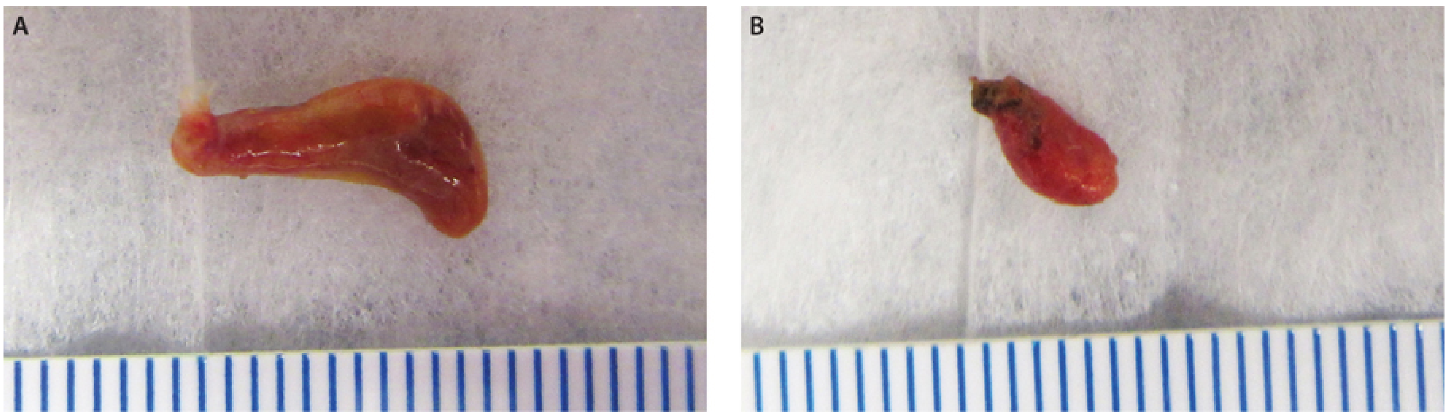

Figure 6-4. Gross photograph of parathyroidectomy specimens in hyperplasia. Two parathyroid glands (A, B) of a patient with secondary hyperplasia are diffusely enlarged, with smooth external surfaces and no normal gland identified.

IV. Dissection techniques: step-by-step description

1. How to orient parathyroid resection specimens

Parathyroid biopsies consist of small fragments that do not require orientation.

Parathyroidectomy specimens should be examined to identify the hilum of the gland. This is important to determine the plane of section to ensure identification of nontumorous parathyroid tissue in a gland with a neoplasm.

Central compartment and thymectomy specimens should be examined to identify all nodular tissues within the fat of these structures.

2. Resection margin documentation

Glands removed for infiltrative neoplasms require resection margin evaluation. Ink the outer surface of the specimen; apply acetone/acetic acid to fix the ink, then pat and air dry.

3. Measurements

Specimens should be measured to provide the size in three dimensions. Although the weight of a biopsy is not required, all parathyroidectomy specimens should be weighed.

4. External examination

The external surface of the gland may have adhesions.

5. Sectioning

The parathyroid gland should be sectioned to include the hilum with sections every 2 to 3 mm. This allows identification of the normal gland, which is usually in the hilum, as well as the lesion. Careful examination of the entire lesion is warranted. Any adherent tissue should be documented.

6. Tissue banking

If tumor is grossly present and a research protocol is available, tissue banking should be considered according to the institutional guidelines. Tissue banking for future studies—such as molecular, flow cytometry, next-generation sequencing (NGS), and other potential research projects—should be considered. Document the "cold ischemia time," if appropriate (varies by institution) and the type of medium used, if any. Collect fresh tissue or snap-frozen tissue for special studies according to protocol. Formalin-fixed paraffin-embedded tissue that is representative of biobanked tissue assists in confirmation of the material studied and, when required, can be repatriated to diagnostic tissue, as occasionally may be necessary for small lesions.

7. Fixation

Fix the specimen for several hours; overnight fixation is not usually required for these small specimens. However, if the specimen includes adjacent or adherent thyroid, this may be required (see chapter on thyroid).

8. Submitting sections

In most cases, the entire specimen should be submitted in serial sections, which allows accurate examination of grossly identified nodules and also permits documentation of nontumorous parenchyma. In the case of a thymectomy and/or central compartment dissection, submission in toto is required to identify any parathyroid tissue.

9. Documentation of sections

Document the gross description and sections as illustrated in section V, below.

V. Gross descriptions using paragraph system

The paragraph system can be used to describe thyroid resection specimens.

Parathyroid biopsy

The specimen identified with the patient's name and as "right inferior parathyroid" consists of a small piece of soft tan tissue that measures 0.1 x 0.1 x 0.1 cm. It is frozen for intraoperative consultation.

1A: Frozen tissue resubmitted

Frozen section diagnosis should be documented in the appropriate field, along with documentation of to whom and what time it was reported.

Parathyroidectomy specimen

The specimen identified with the patient's name and as "right inferior parathyroid" consists of a piece of soft tan tissue that weighs 1.09 g and measures 1.7 x 1.1 x 0.9 cm. It is sectioned and half is frozen for intraoperative consultation.

2A: Frozen tissue resubmitted

2B: Remainder in toto

Central compartment and/or thymectomy specimen

The specimen identified with the patient's name and as "central compartment" consists of a piece of fibroadipose tissue that weighs 2.5 g and measures 1.5 x 1.2 x 0.6 cm.

On section, four nodules are identified; they measure from 0.2 x 0.2 x 0.1 to 0.5 x 0.4 x 0.4 cm.

Section code

3A-D: Nodules in toto

VI. Common pathologic findings

Parathyroid biopsy

Based on the indications for parathyroid biopsy listed above, the following findings are often identified:

- Normal tissue
- Cellular parenchyma

Parathyroidectomy

Based on the indications for parathyroidectomy listed above, the following common pathologic findings are often identified:

- Adenoma
- Hyperplasia

- Carcinoma

VII. Common potential pitfalls and solutions

Parathyroid tissue is difficult to cut on frozen section, and sections often fragment or chatter. The gland normally has abundant fat, and fatty tissue is difficult to cut. Calcified lesions may require decalcification. These problems result in cracked, folded, or torn sections; sections that are missing parts of nodules; and incomplete sections that may be missing the painted resection margin. It is important for the histotechnologists to be aware of these problems to ensure the highest quality sections. It may be necessary to cut deeper levels to obtain full sections.

Occasionally, tissue is displaced during sectioning. Parathyroid tissue requires fresh and sharp blades for sectioning.

As with any other tissue, cross-contamination can be a problem. The bench must be cleaned before a new case is examined, and all instruments must be clean.

Orientation of the lesion can be problematic in complex specimens. If in doubt, the surgeon should be consulted to help with specimen orientation.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

The details of the report should include the following:

- The main pathology identified, usually the nature of the nodule or cyst or the type of inflammatory lesion; include all relevant classifications of morphologic variant, architecture, and cytology, etc
- The location of the lesion
- The size and stage of the lesion
- The growth pattern of the lesion: infiltrative versus encapsulated, widely invasive versus minimally invasive
- Information about lymphatic invasion, angioinvasion, perineural invasion, and extrathyroidal extension
- If multiple lesions are present, identify the secondary and other pathologies
- Number of lymph nodes involved with carcinoma; how many lymph nodes were examined, and how many harbor a metastasis; the size of the largest metastatic focus
- Information about other tissues included in the specimen (eg, thyroid, thymus)
- The procedure that was performed and structures/ organs present

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Acknowledgments, Endocrine section

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7. Ampulla of Vater

Deyali Chatterjee, MD; Huamin Wang, MD, PhD

Resection specimens for ampullary neoplasms are uncommon in daily practice, as ampullary carcinomas account for only 2% of gastrointestinal malignancies. Due to the complex anatomy of the ampullary region, staging of ampullary tumors is very challenging. Thus, proper handling and sampling of ampullary neoplasms in the resected specimens during grossing is of utmost importance in providing clinically useful and relevant information in the pathology report. The purpose of this chapter is to provide a standardized approach to grossing specimens resected for ampullary neoplasms, to assist in optimizing pathologic reporting in compliance with the guidelines provided by the College of American Pathologists (CAP) in their reporting protocol.

I. Complex anatomy of the ampulla of Vater

Ampulla of Vater is a complex structure formed by joining of three histologically distinct anatomic structures: the common bile duct (CBD), main pancreatic duct (MPD; duct of Wirsung), and duodenum. It is surrounded by circularly arranged smooth muscle fibers, which act as a sphincter (named sphincter of Oddi) in controlling the flow of biliary and pancreatic juices (Figure 7-1). Together with the sphincter, ampulla of Vater forms a cylindrical protuberance, called the major papilla, located in the medial aspect of the second portion of duodenum. It is important to keep in mind the complex anatomic variations in the relationship between the CBD and MPD at the major papilla. The classic confluence of CBD and MPD exists in 60% of cases. In 38% of cases, a double-barreled opening is seen at the papilla, and in 2% of case, the CBD and MPD open separately in the duodenum.[1]

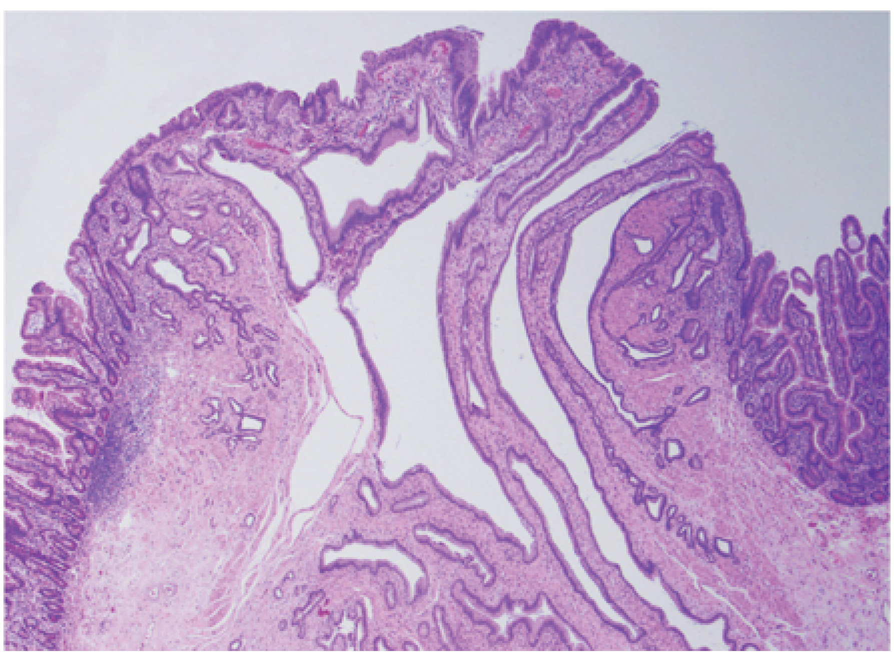

Figure 7-1. Histologic section of ampulla of Vater formed by joining of duodenal mucosa and the confluence of common bile duct and main pancreatic duct which is surrounded by circularly arranged smooth muscle fibers, sphincter of Oddi (H&E, 20x).

II. Definition and subtypes of ampullary neoplasms

The definition of ampullary neoplasm has been controversial. Based on the current World Health Organization (WHO) classification, ampullary neoplasms should be reserved only for the neoplasms that are

either centered on the ampulla of Vater and circumferentially surround it or those that completely replace the ampulla.[2] When a carcinoma is clearly centered in an adjacent structure and only extends peripherally to involve the ampulla, the carcinoma should be classified as primary carcinoma of the adjacent organ, eg, duodenal adenocarcinoma, or pancreatic ductal adenocarcinoma. Ampullary neoplasms may arise from the duodenal mucosa overlaying the ampulla of Vater (periampullary duodenal type) or from the mucosa of the confluence of CBD and MPD in the ampulla (intraampullary type), or may involve both the intra-ampullary and periampullary regions (mixed type).[2-4] When the tumor is big, it is sometimes impossible to specify if the tumor is intraampullary or periampullary in origin. Such tumor is best classified as “mixed” intraampullary/periampullary. In rare cases, in spite of the best efforts, it may be impossible to determine the origin. In such cases, the tumor should be categorized as “tumor site cannot be determined.”

Based on the current CAP cancer protocol for carcinoma of the ampulla of Vater, ampullary carcinoma should be further classified histologically into intestinal type, pancreaticobiliary type, or mixed type (Figure 7-2). The distinction between these two subtypes based on morphology alone can be challenging, and immunohistochemistry may be helpful. Intestinal-type tumors are typically positive for CK20 or CDX2 or MUC2, but negative for MUC1; or are positive for CK20, CDX2, and MUC2, irrespective of the MUC1 staining. Pancreatobiliary-type tumors are positive for MUC1 and negative for CDX2 and MUC2, irrespective of CK20 staining.[5] The pancreaticobiliary-type adenocarcinomas are more aggressive and are associated with shorter survival compared to the intestinal type.

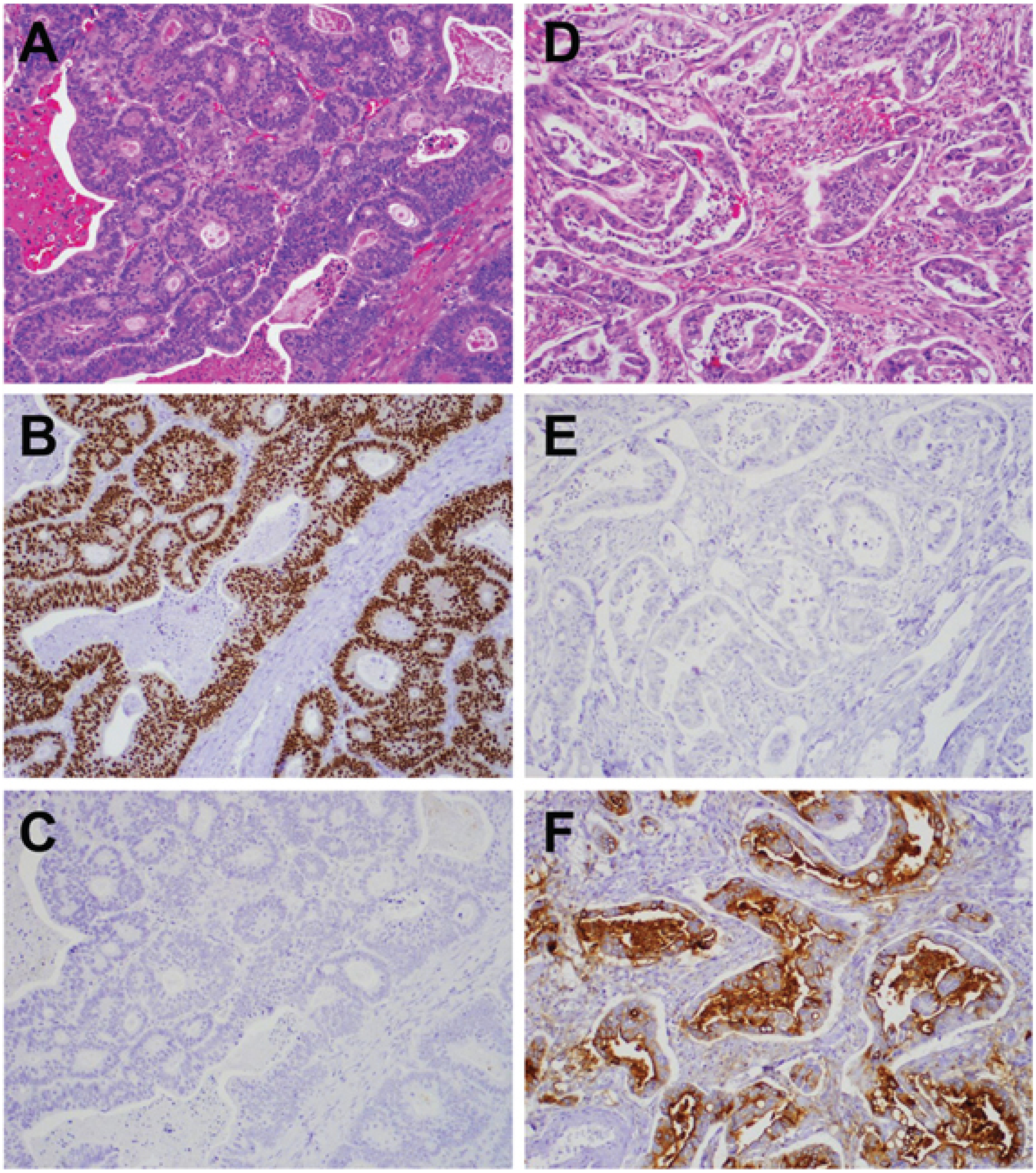

Figure 7-2. Representative photomicrographs showing ampullary adenocarcinoma of intestinal type (A), which is positive for CDX2 (B) and negative for MUC1 (C); and ampullary adenocarcinoma of pancreaticobiliary type (D), which is negative for CDX2 (E) and positive for MUC1 (F). A and D, H&E, 100x.

III. Specimens and indications for the procedures

Ampullary specimens include endoscopic papillectomy, ampullectomy, and pancreaticoduodenectomy (Whipple resection). Historically, all lesions of the ampulla were treated with radical surgery (pancreaticoduodenectomy/Whipple procedure). Due to the complex anatomy of the region arising from the close apposition and confluence of several structures of the pancreaticobiliary tree and gastrointestinal tract, such a radical approach is still considered the gold standard for surgical treatment with curative intent. However, due to the morbidity associated with this procedure and the advances in medical knowledge and technology, less radical approaches, such as endoscopic papillectomy and surgical ampullectomy, have been shown to be feasible and, in selected cases such as benign lesions, superior to the radical approach.[6,7]

The therapeutic role of endoscopic papillectomy for early/small ampullary neoplasms is still controversial.[8] Adenomas or small tumors limited to the duodenal mucosa and without any lymphovascular invasion may be cured by this procedure. However, a tumor may be underestimated by endoscopic and radiologic procedures

alone, especially when the tumor location is deeper. Often, there is a significant chance of incomplete excision due to higher stage (submucosal invasion and beyond), or the tumor can be histologically aggressive, with other adverse histologic parameters such as lymphovascular invasion, which should necessitate more extensive resection. Radical surgery will maximize the chance of complete resection and provide accurate information on the status of regional lymph nodes and staging.

Although the role of neoadjuvant therapy in ampullary cancer is not well defined, recent studies show that this modality can be used as an alternative strategy to improve survival.[4]

IV. Primary tumor staging of ampullary carcinoma

According to the 8th edition American Joint Committee on Cancer (AJCC) staging for carcinoma of ampulla of Vater, the primary tumor (pT) stage of ampullary carcinoma is determined based on the extent of invasion: tumor limited to ampulla of Vater or sphincter of Oddi (T1a), tumor invasion beyond the sphincter of Oddi into the duodenal submucosa (T1b) or muscularis propria (T2), the depth of tumor invasion (up to 0.5 cm or more) into the pancreatic parenchyma or tumor invasion into peripancreatic/periduodenal soft tissue or duodenal serosa (T3a or T3b, respectively), and involvement of adjacent structures such as the celiac axis or superior mesenteric artery and/or common hepatic artery etc (T4). Thus, careful and extensive sampling of the ampullary tumor, taken radially along the long axis of the ampulla with adjacent structures, is of paramount importance.

V. Grossing of endoscopic papillectomy

Endoscopic papillectomy is now an accepted local resection mainly for sporadic ampullary adenoma to minimize surgery-related morbidities. This procedure uses the saline lift technique to resect the adenoma, the duodenal mucosa, and submucosa in the area that is anatomically attached to the ampulla of Vater, including the tissue around the orifice of the bile duct and pancreatic duct.[9] Depending on the technique, the specimen may be received either piecemeal or as one intact piece of adenoma with surrounding mucosa similar to the endoscopic mucosal resection (EMR) specimens. When the specimen is received as one intact piece, care needs to be taken to identify the deep and peripheral margins. The deep and peripheral margins should be inked and the specimen serially sectioned and entirely submitted, with the two most lateral tips in one or two separate blocks to evaluate the presence or absence of adenomatous epithelium at the peripheral margin.

VI. Grossing of ampullectomy

Ampullectomy is a minimally invasive method of treating mucosal and sometimes superficial submucosal lesions or inflammatory conditions of the ampulla of Vater and surrounding periampullary region, which would otherwise require pancreaticoduodenectomy (Whipple procedure). Ampullectomy may be performed endoscopically or surgically through a duodenotomy (transduodenal surgical ampullectomy).[10-12] It would be ideal for the surgeon to orient the specimen to the pathologist handling the specimen since identification of the various margins may be extremely difficult in these specimens. The margins include the radial/deep, the pancreatic duct margin, the bile duct margin, and the peripheral duodenal mucosal margin. The margins should be carefully inked. When possible, the pancreatic duct and the bile duct margins should be submitted first and then the specimen is serially sectioned, either parallel or perpendicular to the long axis of the ampulla of Vater, and entirely submitted.

VII. Grossing of pancreaticoduodenectomy for ampullary neoplasms: step-by-step description

Pancreaticoduodenectomy specimen consists of the head of the pancreas, common bile duct, duodenum, and proximal part of jejunum. Gastric antrum is present in the conventional procedure but is absent in pylorus-preserving pancreaticoduodenectomy. The gallbladder may be attached to the main specimen or may be submitted as a separate specimen.

1. For the pancreaticoduodenectomy specimens, the following five margins should be submitted: pancreatic parenchymal margin (also known as pancreatic neck margin), common bile duct margin, retroperitoneal margin (also known as uncinate margin or superior mesenteric artery margin), proximal gastric/duodenal margin, and distal small intestinal margin. Detailed descriptions of specimen orientation, identification of the margins, and

intraoperative frozen sections for pancreaticoduodenectomy specimens have been described in the chapter (Handling of the Resection Specimens, Staging, and Reporting of Pancreatic Exocrine and Endocrine Neoplasms).

2. Ink the duodenal serosal surface in the tumor area and ink the retroperitoneal margin. Retroperitoneal tissue is rich in adipose tissue, nerve bundles, and lymphovascular channels, and grossly unappreciated microscopic foci of carcinoma can be found infiltrating very close to this margin. At most institutions, retroperitoneal margin is entirely submitted perpendicularly for permanent sections after overnight fixation.

3. Open the small bowel along the opposite side of the pancreas and ampulla of Vater and the stomach along the greater curvature.

4. Inspect the gastric mucosa, duodenal mucosa, and ampulla of Vater for any lesion(s) or tumor and measure the size of the mucosal lesion(s) or tumor.

5. Sectioning of the head of the pancreas: For ampullary neoplasms, we recommend to use the "bivalving" approach, in which the head of the pancreas is bivalved at a plane that goes through both MPD and CBD after inserting a probe in CBD and a probe in MPD to the ampulla of Vater, cut the pancreas in a butterfly fashion along the probes to the ampulla of Vater, and open the CBD (Figure 7-3). This will provide the best visualization of the tumor epicenter and its relationship with the ampulla of Vater, duodenum, CBD, pancreas, and peripancreatic adipose tissue.

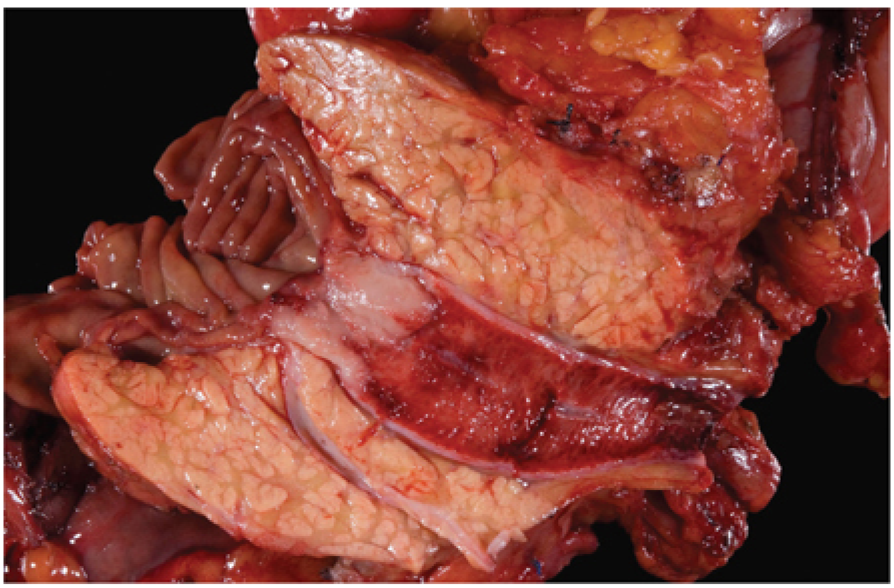

Figure 7-3. A gross photo of an ampullary adenocarcinoma that is epicentered in the ampullary duct (intraampullary type). The common bile duct is dilated and otherwise unremarkable. The pancreatic duct and rest of pancreatic parenchyma and duodenal mucosa are grossly normal.

6. Determine the gross location of the tumor epicenter: The epicenter of the gross tumor is the key to establish the primary site of origin and should be clearly documented in the gross description of the tumor. For ampullary carcinoma, the tumor is either centered on the ampulla of Vater and circumferentially surrounding it or has completely replaced the ampulla. Ampullary carcinoma should be differentiated grossly from primary duodenal carcinoma, which often forms a duodenal mucosal-based polypoid or ulcerated mass with no or only partial involvement of ampulla of Vater or pancreas; from carcinoma of the CBD, which typically forms a concentric mass around the bile duct; and from pancreatic ductal adenocarcinoma, which should have an epicenter in the head of pancreas.

7. The ampullary neoplasm should be sectioned and submitted radially along the long axis of ampulla of Vater and distal CBD to include the ampullary tumor with distal portion of the CBD, MPD, duodenum, surrounding pancreas, and peripancreatic/periduodenal soft tissue and serosa if possible. Serial radial sections of

the ampullary neoplasm with the adjacent structures will clearly demonstrate the depth and extent of tumor invasion (pT stage).

8. If the patient received neoadjuvant therapy, an ulcer or a scar (treated tumor bed) may be the only gross finding, and the ampullary tumor may not be grossly visible. In this situation, the ulcer or scar at the ampulla of Vater should be radially sectioned along the long axis of ampulla of Vater and CBD and entirely submitted as mentioned above. The remainder of the CBD and the head of pancreas is serially sectioned at 3- to 5-mm interval for any possible tumor. If no gross lesion is identified in the CBD and the head of the pancreas, representative sections from the pancreas and CBD should be submitted. However, if no residual tumor is identified in the entirely submitted ampullary region and in the initial representative sections from CBD and pancreas, it is recommended that the rest of the pancreas and CBD should also be submitted for histologic examination to rule out microscopic foci of residual carcinoma in the CBD or pancreatic head.

9. Tissue banking: If requested, tissue harvesting and processing of tumor and normal tissue samples for tissue bank should be performed according to the institutional tumor bank guidelines and the corresponding research protocol.

10. Sampling lymph nodes: Special care needs to be taken to look for lymph nodes in the peripancreatic, periduodenal, and perigastric soft tissue. All possible lymph nodes should be entirely submitted for histologic examination, except grossly positive lymph nodes, from which representative sections are acceptable to document the tumor involvement. Other than those that are present in the specimen, the separately submitted lymph nodes along the hepatic artery and portal vein are also considered regional. Some authors have practiced an orange-peel approach (to strip off all soft tissue around the pancreatic head) to increase the yield of lymph nodes from pancreaticoduodenectomy specimens.[13] Based on the current CAP protocol and *AJCC Cancer Staging Manual,* histologic evaluation of a minimum of 12 lymph nodes is recommended for optimal pN staging for ampullary carcinoma.

VIII. Gross descriptions using paragraph system

1. As described in the previous chapters, Raymond's paragraph system will be used to describe the pancreaticoduodenectomy specimens.

First paragraph describes all components in the pancreaticoduodenectomy specimen and the size of each component.

Second paragraph describes the ampullary tumor: the location of tumor (periampullary, intraampullary, or mixed intraampullary/periampullary involvement), tumor size, nature (solid vs cystic), circumscription, the cut surfaces (consistency, necrosis, hemorrhage), tumor involvement of duodenal mucosa, muscle wall, the MPD, CBD, pancreas, peripancreatic tissue, periduodenal tissue or other structures, such as stomach, omentum etc, and the distance of tumor from all margins.

Third paragraph describes any secondary gross findings in the stomach, duodenum, CBD, and pancreas, and gallbladder if present.

Fourth paragraph describes the ink code, eg, retroperitoneal margin is inked black and serosal surface of duodenum is inked blue.

Fifth paragraph describes the section code.

2. General recommendation for section submission:

a. Sections for the margins: Entirely submit pancreatic parenchymal margin, CBD margin and retroperitoneal margin, representative sections from the proximal gastric or duodenal margin and distal small bowel margin.

b. Representative sections of the ampullary tumor: All ampullary neoplasms should be adequately sampled to include at least one representative section per centimeter of tumor size and sections to document tumor involvement of ampulla of Vater, sphincter of Oddi, duodenal submucosa, muscularis propria and duodenal serosa, CBD, pancreas, peripancreatic and periduodenal soft tissue, etc. To document the depth of direct tumor invasion into the pancreas (T3a vs T3b), full-thickness sections of the tumor with underlying normal pancreatic tissue in the area of deepest invasion into the pancreas should be submitted.

c. Representative sections of any secondary pathology identified in the specimen.

d. One or two representative sections of the uninvolved pancreas and the CBD.

e. Sections of all possible lymph nodes.

3. Example of gross description for pancreaticoduodenectomy:

Head of pancreas, duodenum, common bile duct, and distal stomach, pancreaticoduodenectomy (Whipple) procedure: Received is a pancreaticoduodenectomy specimen consisting of the head of pancreas (7.0 x 5.0 x 5.0 cm), duodenum (19.0 cm in length, 2.0 cm in diameter), distal stomach (8.0 cm in length along the greater curvature, 5.0 cm in diameter at the proximal gastric margin), common bile duct (6.0 cm in length, 1.2 cm in diameter).

Located in the ampullary region is an ulcerated tan-pink solid tumor, 3.0 x 2.5 x 1.5 cm. Grossly, the tumor is centered at the ampulla of Vater and replaces the entire ampulla of Vater. The tumor invades the duodenal wall in the periampullary region and into the head of the pancreas, but no involvement of peripancreatic soft tissue or duodenal serosal surface is identified grossly. The tumor is located at 4.5 cm from pancreatic parenchymal resection margin, 5.0 cm from the common bile duct margin, 2.1 cm from retroperitoneal margin, 12.0 cm from the gastric resection margin, 14.0 cm from distal small bowel resection margin.

The common bile duct is probe patent and dilated with a maximal diameter of up to 1.2 cm. The uninvolved pancreas, mucosa and wall of common bile duct, stomach, and rest of the duodenum are unremarkable. Multiple possible lymph nodes are identified in the peripancreatic soft tissue and perigastric adipose tissue. Gross photographs of the specimen and the tumor are taken. Portion of the tumor, normal duodenal mucosa and pancreas are submitted to tissue bank.

Ink code

Retroperitoneal margin: black

Duodenal serosal surface in the tumor area: blue

Section code

A1: Pancreatic parenchymal margin, en face, entirely submitted for frozen section and permanent section

A2: Common bile duct margin, en face, entirely submitted for frozen section and permanent section

A3: Representative section from the proximal gastric margin, en face

A4: Representative section from distal small intestinal margin, en face

A5-A11: Retroperitoneal margin, perpendicular, entirely submitted

A12-A15: Full-thickness sections of tumor with deepest invasion through duodenal wall into pancreatic parenchyma (A12-A13, one full-thickness section; A14-A15, one full-thickness section)

A15-19: Representative sections of tumor (radial sections) with adjacent duodenal mucosa, common bile duct, pancreas and peripancreatic soft tissue

A20-A21: Representative sections of tumor with periduodenal soft tissue and serosa

A22-A24: Additional sections from tumor

A25: Representative sections of uninvolved pancreas

A26: Representative sections of common bile duct

A27-A29: Four possible peripancreatic lymph nodes in each cassette

A30-31: Four possible peripancreatic lymph nodes

A32-A33: One possible peripancreatic lymph node in each cassette, trisected

A34-A35: One peripancreatic lymph node, serially sectioned, entirely submitted

A36-A38: Four possible perigastric lymph nodes

IX. Common potential pitfalls and solutions

1. Difficulty in determining the site of origin: Due to complex anatomy in pancreaticoduodenectomy specimens, it can be difficult to determine the primary site of origin, especially in large tumors. Differentiating true ampullary carcinomas from duodenal adenocarcinomas, carcinomas of the head of pancreas, and cholangiocarcinoma of the distal common bile duct is critical, as the staging, prognosis, and treatment are different among these tumors.[14,15] This can be achieved in most cases by identifying the location of the tumor epicenter on gross examination and careful histologic evaluation of the extent of tumor involvement of ampulla

of Vater, duodenum, CBD, and pancreas. In rare cases of ampullary carcinomas, especially in patients who received neoadjuvant therapies and had excellent treatment response, this task can be extremely difficult if not impossible. Careful review of the endoscopic and radiologic findings and correlation of histopathologic findings with clinical information may be needed to accurately determine the primary site.

2. The ampulla of Vater is surrounded by circular smooth muscle fibers, known as the sphincter of Oddi. Differentiation from the muscularis propria of the duodenum is necessary for staging purposes and can be a pitfall. The muscle fibers of the sphincter of Oddi surround the distal common bile and pancreatic ducts, as they pass through the wall of the duodenum. As shown in Figure 7-4, the muscle fibers of the sphincter of Oddi are thin and delicate, and arranged in a poorly organized fashion compared to the thick well-orientated muscle bundles in muscularis propria of the duodenum.

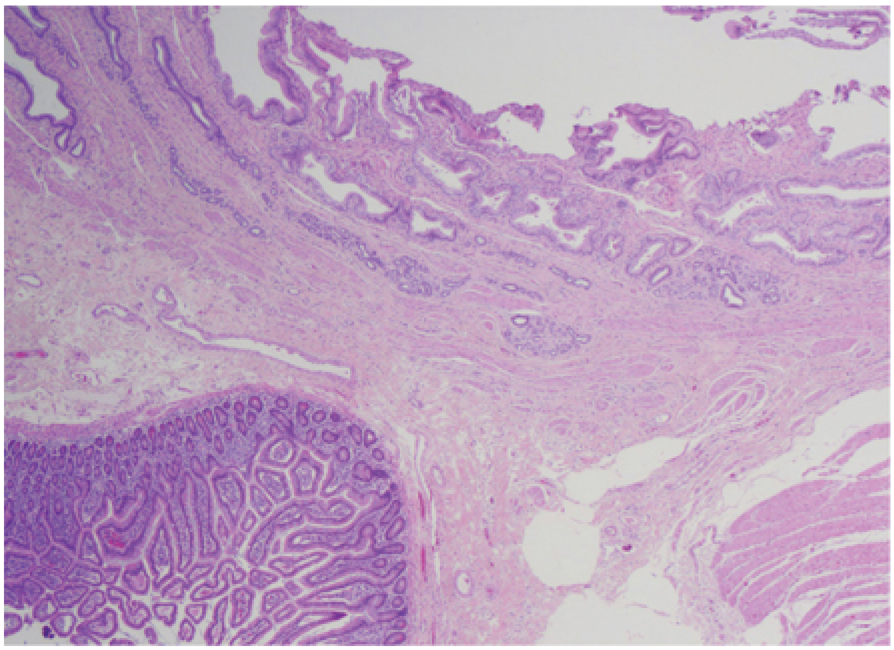

Figure 7-4. Representative photomicrograph showing the sphincter of Oddi that consists of delicate smooth muscle fibers arranged in a poorly organized fashion compared to the thick, well-orientated muscle bundles in muscularis propria of the duodenum.

X. What to include in the pathology report?

The following parameters should be included in the final pathology report.

1. Procedure: Ampullectomy vs pancreaticoduodenectomy (Whipple resection) or other procedure (specify).

2. Tumor Site: Intraampullary [arising from an intraampullary papillary-tubular neoplasm (IAPN) or ampullary ductal (pancreaticobiliary-type)] vs periampullary/ampullary duodenal (arising from duodenal surface of the papilla), mixed intraampullary and periampullary type, or cannot be determined.

3. Tumor Size: Greatest dimension in centimeters and additional dimensions in centimeters vs cannot be determined.

4. Histologic Type: The histologic type based on the current WHO classification should be reported. For adenocarcinoma, the histologic subtype (pancreaticobiliary type vs intestinal type) should also be reported.

5. Histologic Grade: G1: Well differentiated, G2: Moderately differentiated, G3: Poorly differentiated, or GX: Cannot be assessed.

6. Tumor Extension: Tumor limited to ampulla of Vater or sphincter of Oddi vs invades beyond sphincter of Oddi into duodenal submucosa, muscularis propria of the duodenum, directly invades pancreas up to 0.5 cm or more than 0.5 cm into pancreas, extends into peripancreatic soft tissues, periduodenal tissue, duodenal serosa, and/or other adjacent organs or structures such as stomach, gallbladder, omentum, celiac axis, superior mesenteric artery, common hepatic artery, etc.

7. Margin Status: For ampullectomy specimens, the deep (radial) margin and duodenal mucosal margins and the distance of invasive carcinoma from closest margin in millimeters should be reported. For pancreaticoduodenectomy specimens, the pancreatic neck/parenchymal margin, CBD margin, proximal gastric or duodenal margin, distal duodenal or jejunal margin, retroperitoneal/superior mesenteric artery margin and its distance from the closest invasive carcinoma in millimeters should be reported. If applicable, other margin, eg, superior mesenteric vein resection margin, should also be reported.

8. Lymphovascular Invasion

9. Perineural Invasion

10. Regional Lymph Nodes: Number of lymph nodes examined and number of lymph nodes involved by tumor.

11. Pathologic Stage Classification: Primary tumor (pT), regional lymph nodes (pN), and distant metastasis (pM) based on the current *AJCC Cancer Staging Manual.*

12. Additional Pathologic Findings

13. Ancillary Studies

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8. Anus and Perianal Skin

Melissa W. Taggart, MD

Introduction

Because of the relative rarity of some tumors in the anus and perianal skin and subsequent treatment strategies, specimens for tumors of the anus and perianal skin are fairly uncommon.[1,2] The anus is a complex structure with variable types of tissue; therefore, a number of different neoplasms can arise in this area (Figure 8-1).[3,4] Most malignant tumors in this area represent squamous cell carcinomas, with the majority driven by infection with human papillomavirus (HPV).[5,6] Occasionally, primary or secondary adenocarcinomas can be seen, including those arising the colorectal-type mucosa of the proximal anus (mucosal-derived adenocarcinoma, sometimes in association with mucosal neoplasia [adenomas] or with pagetoid spread [secondary extramammary Paget disease]), tumors from extramucosal areas (anal gland adenocarcinoma, fistula-associated adenocarcinoma, or non-anal gland, non–fistula-associated adenocarcinoma), or those arising in the perianal skin (primary extramammary Paget disease or non–Paget-type carcinoma from skin adnexa). Other primary tumors, such as neuroendocrine carcinoma, mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN), and undifferentiated carcinoma, can occur in the anus. Basal cell carcinoma in the perianal skin can also be seen.[7] For anal and perianal tumors, location of the tumor, size, involvement of adjacent organs, and metastases to regional lymph nodes are the most important factors for pathologic staging.[8]

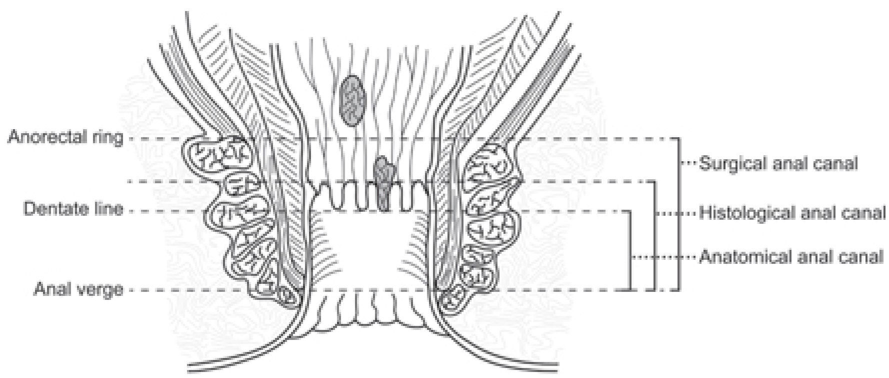

Figure 8-1. Anatomy of the anal canal. The surgical anus extends from the proximal border of the anorectal ring (puborectalis muscle and internal/external spincters) to the mucoepidermal junction at the anal verge. Lesions below the anorectal ring would be classified as an anal tumor. The dentate line delineates squamous mucosa from colorectal type columnar or transitional mucosa. Perianal glands are located in this area of the anus.

The following represents recommendations for adequate gross and intraoperative assessment of anal and perianal specimens to provide an appropriate representation of the processes occurring in the specimen and sampling to furnish information needed to fulfill College of American Pathologists (CAP) protocol requirements and direct subsequent treatment.[9]

I. Indications for different types of anal/perianal skin resections

Tumors of the anus and perianal skin can be resected by local excision or by more extensive abdominoperineal resections. In general, most squamous lesions of the anus are not formally resected and can be treated with (chemo-)radiation therapy.[10] Early squamous neoplasia of the anus, basal cell carcinoma of the perianal skin, and extramammary Paget disease may be locally excised.

For resistant or recurrent squamous cell carcinoma and other carcinomas (adenocarcinoma, neuroendocrine carcinoma, MiNEN, and undifferentiated carcinoma), an abdominoperineal excision (or more extensive surgery, such as other en bloc organ resections or pelvic exenteration) may be performed.

Because of differences in lymph node drainage and treatment strategies, distinguishing rectal tumors from those arising in the anus and those arising from the anus and perianal skin is important. Unfortunately, this distinction may need clinical correlation, especially for localized excisions. The surgical anus begins at the anorectal ring, corresponding to the palpable proximal border of the puborectalis muscle on digital rectal examination (Figure 8-2). Tumors are considered as rectal if the inferior margin of the tumor is less than 16 cm from the anal verge or if any part of the tumor involves the intestine at least partially supplied by the superior rectal artery.[11] When distal to these landmarks, the tumor is considered as arising from the anus, perianal skin, or skin. The anus ends at the mucoepidermal junction, characterized histologically by epidermal appendages. Additional clinical information, such as complete visualization of the tumor with gentle traction of the buttocks and distance of the lesion from the anus, can further delineate these distal lesions (Figure 8-3).

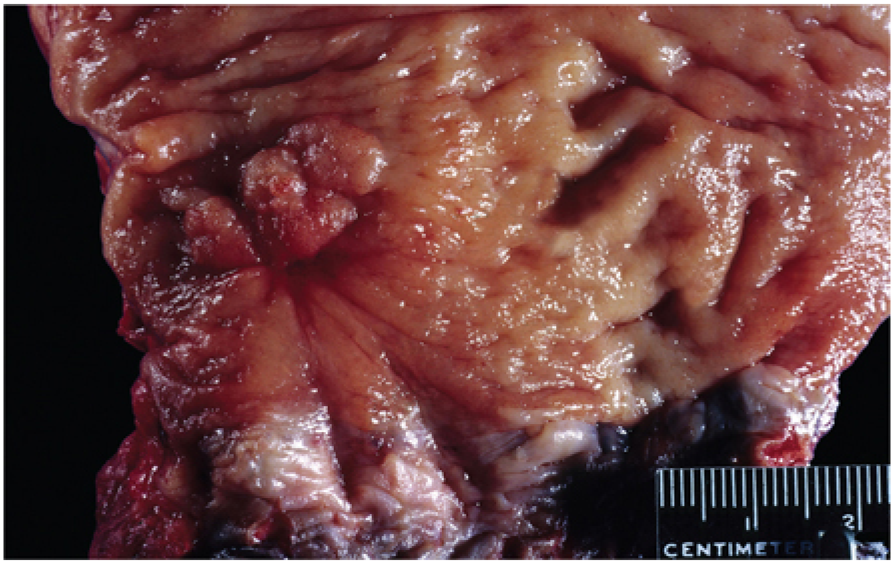

Figure 8-2. For this treated adenocarcinoma, clinical information may be needed to determine if this adenocarcinoma represents a rectal or anal primary.

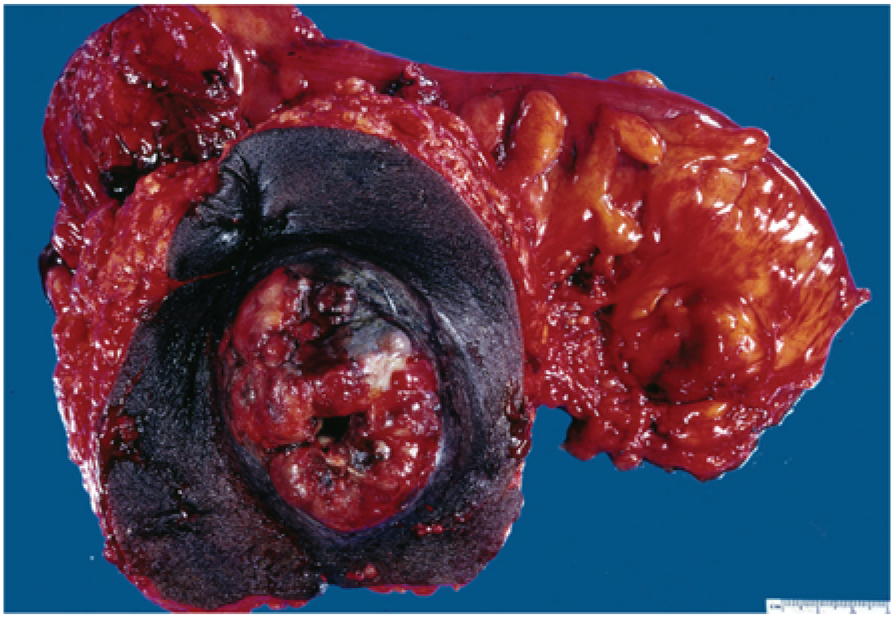

Figure 8-3. Clinical information may be needed to determine if this squamous cell carcinoma represents a tumor of the anus or perianal skin, as perianal cancers are within 5 cm of the anus and can be completely visualized with gentle traction on the buttocks.

A total proctocolectomy may be required for patients with polyposis syndrome or idiopathic inflammatory bowel disease of long duration or with development of neoplasia.

II. Specimen orientation, lesion identification, and evaluation of margins

Proper fixation allows for optimal sectioning of anal/perianal skin specimens; however, orientation of the specimen and evaluation of the margins should be performed in the fresh state. Occasionally, other adhered organs may be included with a specimen, and the relationship of the tumor to these areas along with margin assessment of the adhered organ/structure (if applicable) should be documented.

Localized resections may be submitted pinned on cork and may or may not be oriented. These resections should be (differentially, if oriented) inked and submitted according to the orientation so that all peripheral and deep margins can be assessed. Occasionally, these specimens may be submitted by the surgeon in a piecemeal fashion, with or without further orientation. In these unoriented specimens, only peripheral tissue edges and deep margins can be assessed, and the findings will need to be clinically correlated.

Abdominoperineal resections (or more complex specimens) should be opened along the long axis before fixation, using manual palpation to direct the incision to the uninvolved wall of the specimen, if the tumor is not circumferential. Often intraoperative assessment consists of gross evaluation of the closest intestinal margin. Only rarely is frozen section assessment needed, which is generally case specific. When assessing distal margins of proctectomy specimens when only a scar remains, palpation may be helpful, and evaluation of the closest approach of fibrosis to the margin is prudent. After neoadjuvant therapy, the tumor bed may be difficult to identify, and clinical information may be helpful for localization.

The specifics of the tumor site should be determined including the position of the tumor in anus/perianal skin and laterality. Before sectioning, the tumor size in two dimensions should be noted as well as the distance to the proximal and distal margin.[8]

After fixation, the tumor should be serially sectioned to determine the depth of invasion (measurement of the deepest aspect and estimation of the level of involvement) and evaluation of the closest radial margin. Other lesions in the nontumoral anorectum and skin (diverticula, polyps, inflammatory changes, fistula, nevi, etc) should be noted.

IV. Tissue banking

Samples of fresh tumor and/or normal mucosa can be performed according to institutional review board (IRB)-approved or patient-consented requests. Harvesting should be performed as soon as possible to decrease ischemic time. The protocol may require frozen section to confirm histology.

IV. Lymph node dissection

Involvement of lymph nodes by metastatic disease is crucial for determining stage and adjuvant therapy. After submission of relevant tumor sections, the remaining soft tissue can be dissected for lymph nodes. This is performed by the manual method (sectioning, sight, and palpation) or by the use of fat-clearing reagents (graded alcohol solutions followed by xylene solution).[12] Fat-clearing solutions increase expense and toxicity to the prosector by use and disposal of solutions. In addition, the effect on immunohistochemistry (if needed) is not completely known.[12,13] Many factors (including preoperative therapy) can decrease lymph node yields.[14,15]

All lymph node candidates should be submitted (grossly negative nodes in their entirety; and, in the untreated tumor, grossly positive lymph nodes may be submitted representatively). Pathologists should make every attempt to find all lymph nodes, and these attempts should be documented.[13,16] Larger lymph nodes should be serially sectioned.

V. Grossing of anal/perianal specimens

1. Localized excisions

Localized resections may be submitted pinned on cork and may or may not be oriented.

a. The tissue should be measured and described, including tissue integrity, lesion details (lesion size and configuration, presence of ulceration), and distance to peripheral margins.

b. If oriented, the specimen should be differentially inked. Occasionally, these specimens may be submitted by the surgeon in a piecemeal fashion, with or without further orientation.
c. The tissue should be serially sectioned.
d. The lesion depth should be assessed qualitatively and quantitatively.
e. The tissue should be submitted according to the orientation so that all peripheral and deep margins can be evaluated, allowing for quantitative margin assessment. All relevant tissue should be submitted for processing.

2. Abdominoperineal resections

a. Note and measure all portions of the intestine, anus, and skin and any additional organs removed with the specimen.
b. Orient the specimen and ink the soft tissue margins in the area of the tumor.
c. If present, remove the staple line at proximal intestine, cutting as close to the staple line as possible.
d. Open the specimen longitudinally (generally distal to proximal), using digital palpation to guide the cut the side opposite to the tumor if possible. If the tumor is circumferential, guide the incision away from any adherent organs or structures.
e. Visualize the lesion, measuring the tumor in two dimensions and noting the characteristics of the tumor (size, configuration [flat, sessile, polypoid, ulcerated]), amount of and location of luminal involvement (anterior, posterior, right/left lateral), and any adjacent/related lesion (condyloma, scar, tattoo pigment) and tumor location to specimen landmarks (rectum, dentate line). Measure the distance from the tumor to the margins before fixation.
f. Assess tumor relationship to adhered organs if present.
g. Provide gross intraoperative assessment or sample as needed for frozen section evaluation, if requested.
h. Examine the remainder of the specimen (including uninvolved areas of the intestines and other organs) and annotate any abnormalities.
i. Pin and fix the specimen, generally overnight for proper fixation and to prevent shrinkage.
j. Sample margins (proximal and distal intestinal, mesenteric and/or vascular pedicle, and those of any adhered organ or structure). When sampling intestinal margins, the entire wall with mucosa and surrounding soft tissue should be represented in the sections.
  (1) If the tumor is less than 2 cm from a margin, then perpendicular sections showing the closest approach of the tumor to the margin is warranted.
  (2) Otherwise, parallel/en face sections are adequate. Margins far from the tumor may be representatively sampled, while closer margins should be sampled in totality.
k. Serially section the tumor to measure depth of the tumor and assess the relationship of the tumor to radial margin(s) and any adhered structures/organs.
l. Sample the tumor, selecting and annotating sections to show deepest approach of the tumor to closest radial margin, tumor-to-normal or tumor-to-condyloma interface, involvement (or lack of involvement) of adhered organs/structures. See section VI for special considerations.
m. Sample any other lesions in the intestine or adhered organ/structure.
n. Dissect lymph nodes and submit in totality. Grossly involved lymph nodes can be representatively submitted in specimens that have not received neoadjuvant therapy. Lymph node evaluation can be performed by manual methods or using fat clearing agents. The methodology should be noted.
o. General recommendation for section submission for untreated tumors:
  (1) Proximal intestinal margin, distal perianal skin margin, and margins from any adhered organs/structures.
  (2) Representative sections of the tumor, at least one representative section per centimeter of tumor size (minimum of five sections) to include tumor with relationship to closest radial margin(s), tumor-to-normal and/or tumor-to-condyloma interface, and tumor with relationship to adhered organs/structures (if applicable).

(3) Representative sections of any other abnormalities in the specimen. Representative sections of the uninvolved colon can be submitted but are not necessary.

(4) All possible lymph nodes.

VI. Special considerations

1. Neoadjuvant therapy

Preoperative therapy often decreases the size of the tumor. When evaluating gross distance of the tumor to the distal margin, palpation of fibrosis may be helpful, with the distance from the palpable fibrosis instead of the mucosal lesion used as the margin clearance. It may be prudent to submit the entire perianal skin margin for microscopic evaluation for treated anal tumors.

Gross tumor may not be evident and only fibrosis may be seen. If only fibrosis is identified upon serial sectioning, extensive sampling of the tumor bed is needed (with some institutions completely embedding the tumor bed) with preserved relationship of the fibrosis to the closest radial margin. If gross tumor remains, representative sections as described above may be submitted. Lymph nodes may be smaller or present in lower numbers after neoadjuvant chemotherapy.

2. Adherent or fistulized organs or structures/pelvic exenterations

When adhered organs/structures are excised en bloc with the proctectomy specimen, histologic sections should be sampled in the areas of the adhesions/fistula between the tumor and the organ, as well as margins of the adhered organ/structure. In addition to the inclusion of pelvic organs, pelvic exenterations have abundant surrounding soft tissue, which often needs to be sampled thoroughly and with orientation as discerning treatment effect or inflammatory changes from tumor may be extremely difficult. When the soft tissue is fibrotic, lymph nodes may be challenging to locate. In treated tumors, it may be prudent to submit lymph nodes that appear grossly involved by tumor in their entirety or develop a process for resampling if only treatment-related changes remain in the originally submitted sections.

3. Polyposis syndromes

In polyposis syndromes, patients can have thousands of polyps. A reasonable estimate of the number of polyps (count if less than 100) and notation of the distribution within the colorectum should be made. Any lesion with features suspicious for malignancy should be properly sampled, with the location noted and margin evaluation. Polyps over 1 cm should be sampled. Representative smaller polyps from the four quadrants of the colorectum should be sampled in at least one cassette per quadrant.[17] Proper sampling is needed to stage each tumor. In extended proctocolectomies, regional lymph nodes should be separated (as well as the dissected fibroadipose tissue, in the event additional evaluation is needed).

4. Inflammatory bowel disease

The pattern and distribution of inflammatory lesions should be noted. Any raised or mass-forming lesion should be sampled. As in polyposis syndrome, multiple invasive tumors may be present, and proper sampling of the lesion (full-thickness sections with radial margin relationship), as well as regional lymph node sampling, is needed.

VII. Example of grossing description of an intraabdominal colorectal specimen

A. SIGMOID COLON, RECTUM, AND ANUS – Received is an unoriented extended abdominoperineal specimen consisting of the sigmoid colon (15.1 cm in length and 4.0 cm in diameter), rectum (13.2 cm in length and 3.6 cm in diameter), anus (4.1 cm in length and 3.2 cm in diameter), and perianal skin (2.2 cm length and 3.3 cm in diameter) with an ovoid portion of posterior vagina (3.4 x 1.1 x 0.9 cm) adhered to the anterior aspect of the rectum/anus.

Opening the lumen of the intestine and anus reveals an indented scar (3.5 x 2.1 cm) in the anterior and right lateral anus. The epicenter of the scar is 1 cm distal to the dentate line. A palpable lesion in the area of the scar is 25.2 cm from the proximal colonic and 4.2 cm from the anal skin margins. Sectioning of the scarred lesion reveals tan-white firm tissue intermixed with tan friable tissue, which may represent residual carcinoma. The lesion extends to a depth of 1.2 cm. The lesion extends through the wall of the anal wall into the perianal soft

tissue. Fibrosis extends from the deep aspect of the lesion into the distal aspect of the adhered vaginal wall. The tumor is 0.4 cm from the closest peripheral soft tissue margin around the anorectum at the anterolateral aspect and 0.2 cm from the distal vaginal margin.

No other lesions are identified on the serosal surface. There is a 0.8 x 0.7 cm pedunculated polyp in the sigmoid colon, 5.1 cm from the proximal colonic margin. The remainder of the colorectum is free of lesion. The perianal skin is free of lesion. Eighteen lymph node candidates are identified with sectioning and palpation of the mesenteric and pelvic soft tissue, ranging from 0.4 to 1.2 cm. The largest lymph node appears grossly involved by tumor.

The intact and sectioned gross specimen is photographed. Representative tissue from the tumor and normal-appearing anal mucosa are submitted for tissue banking.

Ink code: Black-right aspect of the peripheral anorectal soft tissue and vaginal wall; blue-left aspect of the peripheral anorectal soft tissue and vaginal wall.

Section code

A1: Representative proximal colonic margin, en face

A2-A6: Entire perianal skin margin, en face

A7: Vascular pedicle margin at sigmoid colon mesentery, en face

A8: Distal vaginal margin with closest approach to adhered fibrosis, perpendicular section

A9: Remainder of distal vaginal margin, en face

A10-A12: Entire right peripheral vaginal margin, en face

A13-15: Entire left peripheral vaginal margin, en face

A16: Entire proximal vaginal margin, en face

A17, A18: Closest approach of tumor/fibrosis from peripheral perianal soft tissue at the anterior aspect

A19, A20: Closest approach of tumor/fibrosis from peripheral perianorectal soft tissue at the right lateral aspect

A21-A22: Full-thickness section of the lesion to include perianorectal soft tissue

A23: Lesion with relationship to dentate line

A24: Lesion with relationship to perianal skin

A25-A27: Additional sections of the lesion

A28, A29: Sigmoid polyp bisected, in toto

A30-A33: Four whole lymph node candidates

A34: One trisected lymph node candidate

A35: Representative sections of largest grossly involved lymph node

VIII. Common potential staging pitfalls and solutions

All invasive carcinomas in the anus and perianal skin (within 5 cm of the anus), including squamous carcinoma, adenocarcinoma, neuroendocrine carcinoma, mixed adenocarcinoma neuroendocrine carcinoma/mixed neuroendocrine-nonneuroendocrine tumor, verrucous carcinoma, basal cell carcinoma, and undifferentiated carcinoma, are staged with the same criteria.

T category:

The T category for tumors of the anus and perianal skin relies on the presence of invasion, size of the invasive component, and invasion into adjacent organs such as vagina, urethra, or bladder. Extension of tumor into areas immediately proximal and distal to the anus (ie, rectum and perianal skin) and external anal sphincter are not considered “adjacent organs.”

Most tumors in the anus are squamous cell carcinoma. In low-stage tumors, colonization of existing surface glands/dysplasia involving squamous metaplasia in the proximal aspect of the anus can be mistaken for superficial invasion. Tangential sectioning may also cause difficulty in determining in situ and superficially invasive tumors. Additional step sections may be helpful. Most abdominoperineal resections are performed for either resistant or recurrent squamous cell carcinoma. Issues related to prior treatment included in previous chapters apply here, especially examination of multiple sections near the tissue edge for margin assessment in

near complete or complete regression. Rarely, therapy-related changes in surrounding tissue, such as skeletal muscle, can impart atypia, mimicking carcinoma. Use of immunohistochemical stains aids in the distinction. Exophytic carcinomas grossly resembling warty lesions may need extensive sampling of the base to determine the true nature of the neoplasm.

For adenocarcinomas of the anus, determination of the primary site (rectal vs anal) for adenocarcinomas in the anorectum is necessary for proper staging. These tumors may need correlation with clinical findings before neoadjuvant therapy. Extension into the external anal sphincter is not considered T4 disease for anal carcinomas, as it is in carcinomas of the rectum. Normal perianal glands in the area of the dentate line may extend into the muscularis propria and should not be mistaken for neoplastic glands.

N and M categories:

The N category is based on the location of the lymph nodes containing metastatic tumor rather than the number of positive lymph nodes as in other sites of the gastrointestinal tract. Only mesorectal, inguinal (superficial and deep), superior rectal (hemorrhoidal), and external iliac and internal iliac (hypogastric) lymph nodes are considered regional. Involvement of other lymph nodes is considered distant metastatic disease (M category). In the setting of neoadjuvant therapy, finding adequate numbers of lymph nodes may be challenging. Although there is no targeted minimal number of lymph nodes suggested by the American Joint Committee on Cancer (AJCC), an attempt to find all lymph nodes should be made.[8] Lymph nodes containing only viable-appearing tumor, and not therapy-related changes such as fibrosis, should be considered positive.

IX. Synoptic pathology reporting

The current CAP protocol requires the following parameters to be included in the final pathology report. Synoptic reporting is not required for excisional biopsy (polypectomy), local excision (transanal disk excision), primary resection specimens with no residual cancer (eg, following neoadjuvant therapy), or cytologic specimens.

1. Anal and perianal carcinomas (including high-grade neuroendocrine carcinoma)[9]

- Procedure: Abdominoperineal resection, excisional biopsy, transanal disk excision (local excision, other (specify), not specified
- Tumor Site: Anal canal, perianal region, anus, not otherwise specified, not known, other (specify)
- Tumor Size: Provide at least greatest dimension (centimeters)
- Histologic Type: Use WHO classification of rpithelial tumors of the gastrointestinal tract[7]
- Histologic Grade: G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; G4: undifferentiated; other (specify); GX: cannot be assessed, not applicable
- Tumor Extension: No evidence of primary tumor; carcinoma in situ, tumor invades lamina propria;muscularis mucosae; submucosa; into but not through anal sphincter muscle; into but not through muscularis propria of rectum; through anal sphincter muscle into perianal or perirectal soft tissue without involvement of adjacent structures; or directly invades adjacent structures (specify); tumor invades perianal skin, cannot be assessed
- Margins: Specify assessed margins (may include proximal, distal, radial or mesenteric, deep, mucosal, and others); specify involved margins or the distance of invasive carcinoma, intramucosal adenocarcinoma, high-grade dysplasia, and adenoma from closest margin in mm or cm if all margins are uninvolved
- Treatment Effect: No known preoperative therapy; present (if present, optional scoring of treatment effect can be added using modified Ryan criteria)[9,18]
- Regional Lymph Nodes: Note presence or absence of number lymph nodes submitted or found and number of involved lymph nodes
- Pathologic Stage Classification (pTNM): Staging should be assessed according to guidelines provided by the AJCC 8th edition.[8] Report only pertinent categories based on the available information when the report is issued; if applicable, TNM descriptors should be included (m [multiple primary tumors], r [recurrent], y [posttreatment])

Optional elements include:

- Lymphovascular Invasion: Not identified, present, cannot be determined
- Perineural Invasion: Not identified, present, cannot be determined
- Additional Pathologic Findings
- Ancillary Studies

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9. Appendix

Melissa W. Taggart, MD

The appendix is frequently resected for inflammation (acute appendicitis). Appendiceal neoplasms are rare and uncommonly identified before the appendix has been removed, as many tumors in the appendix are incidentally encountered or present as acute appendicitis.[1] The most common tumor encountered in the appendix is the well-differentiated neuroendocrine tumor, often seen on routine sections of distal aspect of the appendix. Mucinous tumors of the appendix (low-grade appendiceal mucinous neoplasms [LAMN]/ high-grade appendiceal mucinous neoplasms [HAMN]) and their associated spread (mucinous adenocarcinoma peritonei, low or high grade) are increasingly seen, especially as many radiologically detected “mucoceles” are now recognized as low-grade malignant rather than reactive processes.[2] Rare tumors, such as goblet cell adenocarcinoma and mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN), can also be encountered. In these lesions (LAMN/HAMN, goblet cell adenocarcinoma, and MiNEN), more extensive sampling may be required to fully delineate the process and identify high-risk features.[3,4] In addition, tumors with histologic features (mucinous and nonmucinous adenocarcinoma and high-grade neuroendocrine carcinoma) identical to those seen in the colorectum and their associated precursor lesions (tubular/tubulovillous/villous adenoma) are less commonly seen.[5] Occasionally, separation of these tumors from those arising in the cecum can be challenging, and appropriate gross evaluation and histologic sampling is paramount in making this distinction.

The following represents recommendations for adequate gross and intraoperative assessment of appendiceal specimens and associated peritoneal spread to provide an appropriate representation of the processes occurring in the specimen and sampling to provide information needed to fulfill College of American Pathologists (CAP) protocol requirements and direct subsequent treatment.[6,7]

I. Indications for type of resections for appendiceal neoplasms

Not uncommonly, an underlying malignant process is not identified before removal of the appendix unless the tumor forms a large mass or radiologic studies identify a mucinous lesion in the appendix, peritoneal spread, or metastases to visceral organs. Thus, the most commonly encountered specimen is the appendectomy specimen, which is often resected for acute appendicitis. Tumors such as well-differentiated neuroendocrine tumors or goblet cell adenocarcinoma can be obscured by, cause, or even mimic an inflammatory process. If an intraluminal mucinous tumor is suspected preoperatively, the surgeon may excise a portion of the periappendiceal cecum (cecal cuff) with the appendix or perform a limited ileocecectomy if no serosal implants are seen in the region of the terminal ileum/right colon.

Tumors commonly requiring lymph node evaluation (all except for low-stage well-differentiated neuroendocrine tumors and confined LAMN/HAMN) need a more extensive ileocolectomy resection (often in the form of a right colectomy). Unless the tumor is recognized before or during surgery, the right colon may be subsequently resected.

When a mucinous tumor is identified, especially LAMN/HAMN, careful evaluation of the visceral and parietal peritoneum is required by the surgeon. Many centers will perform cytoreductive surgery (CRS) to include all peritoneal surfaces and/or associated organs with peritoneal implants, up to the point of resecting as much of the intraabdominal/pelvic tumor while leaving the patient with adequate organ function and limited morbidity. Cytoreductive surgeries for mucinous adenocarcinoma peritonei (clinically seen as pseudomyxoma peritonei) are often accompanied by hyperthermic intraperitoneal chemotherapy (HIPEC).

II. Specimen orientation, lesion identification, and evaluation of margins

Because of the chance of occult tumors, an attempt to orient the appendix and identify the proximal margin, serosal surface, and radial margins on all appendices should be made. In the intact specimen, gross evaluation of the appendix is straightforward. Generally, the appendix is covered by a serosa except in the region of the mesoappendix. Unfortunately, because of the association with acute appendicitis and adhesions, orientation of

the appendix may be difficult. The appendix may be received disrupted or even fragmented. In these cases, clues to orientation, such as a staple line at the proximal margin, can be helpful. Orientation as to the cut surfaces, which represent additional radial margins (from the dissection of adhesions), and the true mesoappendiceal margin may be difficult or impossible to distinguish. In these incidences, inking the periphery of the appendix may be the only option after evaluation for any identifiable serosal surface. Before incision, the appendix should also be inspected for perforation, exudate, and tumor/mucinous deposits on the serosa, which may be subtle (appearing as red, glistening fine adhesions or small droplets of clear mucin) (Figure 9-1).

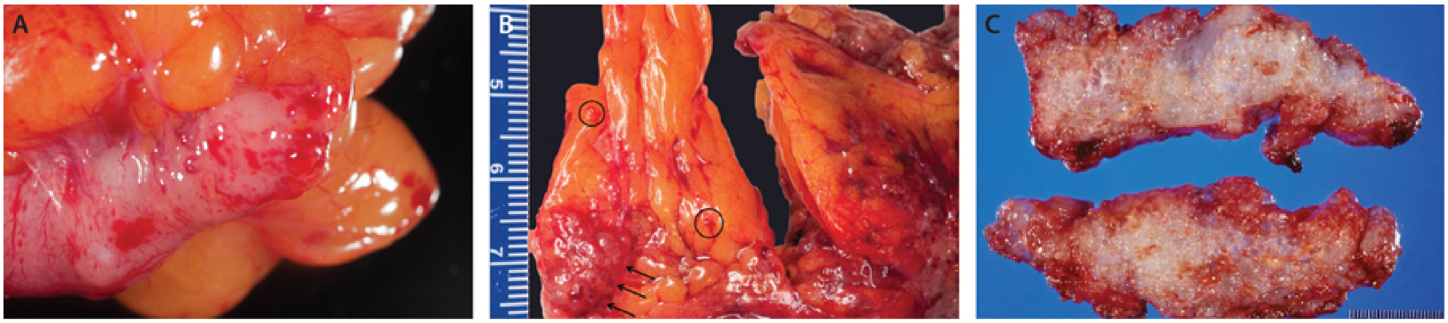

Figure 9-1. A. Mucin forms fine reddish nodules at the tip of this appendix involved by low-grade appendiceal mucinous neoplasm (LAMN). B. This peritoneal soft tissue shows diminutive tumor nodules (circles) as well as more pronounced mass lesions (arrows). C. More extensive involvement of the omentum is seen ("omental cake"), clearly recognizable as intraabdominal spread from a mucinous tumor.

When the process appears to be acute appendicitis, it is prudent to serially section the proximal two thirds of the appendix and longitudinally bisect the remaining distal aspect while looking for mass lesions. Well-differentiated neuroendocrine tumors will appear firm and yellow-tinged. For these tumors, accurate size measurement is a key component when determining further surgical intervention. When a known mucinous tumor is present, the appendix is best fixed in formalin overnight and serially sectioned completely, with the last slice of the tip radially sectioned (Figure 9-2).

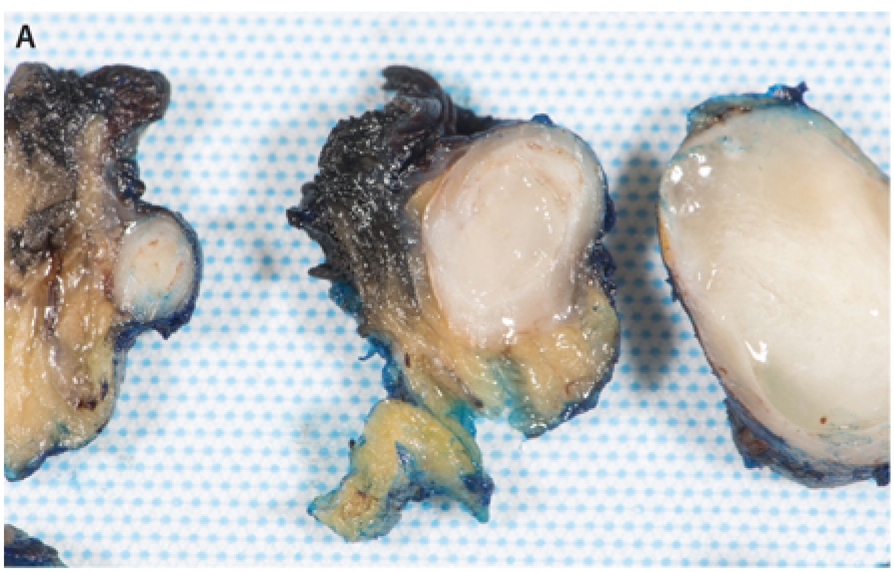

Figure 9-2. Sections of mucinous appendiceal tumor after fixation.

Right hemicolectomy specimens should be fixed overnight before sectioning; however, orientation of the specimen and evaluation of the margins should be performed in the fresh state. The appendix is present at the cecum in the area where the taenia coli converge. Occasionally, an appendiceal tumor will completely obliterate the appendix. Knowledge of the patient's surgical history (history of appendectomy) and inspection of the

appendiceal orifice and surrounding cecal mucosa is helpful to distinguish a cecal primaries, appendiceal primaries, and metastatic foci. Determination of site is based on the location of the bulk of the tumor.[6,8] Margins for right hemicolectomies include the proximal small intestinal, distal colonic, and radial (mesenteric and/or retroperitoneal soft tissue) margins. Serosal-based implants are not uncommonly seen on the serosa of the intestine in patients with appendiceal mucinous tumors. Distance from these lesions, as well as the main tumor, should be noted. Any adherent organs should be documented, and margins from these organs should also be submitted. Other lesions in the nontumoral appendix (diverticula, exudate, etc) and colorectum (diverticula, polyps, inflammatory changes, etc) should be noted.

Often intraoperative assessment consists of gross evaluation of the closest margin; however, frozen section may be required to determine the nature of the neoplastic process.

IV. Tissue banking

Samples of fresh tumor and/or normal mucosa can be performed according to institutional review board (IRB)-approved or patient-consented requests. Harvesting should be performed as soon as possible to decrease ischemic time. The protocol may require frozen section to confirm histology.

IV. Lymph node dissection

After submission of relevant tumor sections, the remaining soft tissue can be dissected for lymph nodes. Identification of soft tissue deposits and involvement of lymph nodes by metastatic disease in the adventitia are crucial for determining stage and adjuvant therapy, especially for non-LAMN/HAMN lesions. Often no lymph nodes are grossly identified on appendectomy specimens. In ileo-/right colectomy specimens, this is performed by the manual method (sectioning, sight, and palpation) or by the use of fat-clearing reagents (graded alcohol solutions followed by xylene solution).[9] Fat-clearing solutions increase expense and toxicity to the prosector by use and disposal of solutions. In addition, the effect on immunohistochemistry (if needed) is not completely known.[9,10] Many factors (including preoperative therapy) can decrease lymph node yields.[11,12] Smaller resections specimens, such ileocolectomy, will have fewer lymph nodes.

All lymph node candidates should be submitted (grossly negative nodes in their entirety; and, in the untreated tumor, grossly positive lymph nodes may be submitted representatively). Pathologists should make every attempt to find all lymph nodes, and these attempts should be documented.[10,13] Larger lymph nodes should be serially sectioned.

V. Grossing of specimens for appendiceal neoplasms

1. Appendectomy

a. The appendix should be measured and described, including tissue integrity, variations in diameter, perforations, and serosal changes (exudate, hyperemia, mucinous/tumor implants, nodularity). If present, the mesoappendix should be measured and its serosal surface should be evaluated similarly. The presence of a cecal cuff should be noted.

b. The serosal and cut surfaces should be differentially inked, if possible. Otherwise, it may be prudent to ink the entire surface.

c. If a staple line is present at the proximal margin (either appendiceal base or cecal cuff), then the staple line should be carefully removed with the incision as close to the staple line as possible.

d. If no clear mass lesion is seen, the appendix can be serially sectioned from the proximal to distal aspect, leaving the last 1 cm to 2 cm of the appendix intact. This portion can be longitudinally sectioned.

e. If a solid mass or mucinous neoplasm is identified or suspected before sectioning, then the appendix should be fixed overnight and completely sectioned in a serial manner with the last section of the tip radially sectioned.

f. Document details of the lesion/mass including description of lesion (size, mucinous/solid consistency, involvement of mucosa, depth of invasion [qualitatively and quantitatively] by tumor and/or mucin, relationship to any perforation or serosal lesions), and distance of lesion to margins.

g. General recommendation for section submission:

(1) If no clear mass/lesion is identified, then the designated proximal margin should be submitted en face to include all layers of the cecal/appendiceal wall and surrounding soft tissue. Representative cross-sections with mesoappendiceal margin and longitudinal sections of the tip should be submitted.

(2) If a distinct mass/lesion is seen, then the designated proximal margin should be submitted en face to include all layers of the cecal/appendiceal wall and surrounding soft tissue. In the unlikelihood that the mass/lesion is less than 1 cm from the proximal margin, then representative perpendicular sections could be considered, with the remainder of this margins submitted en face.

(3) Often solid tumors in the appendix are small enough to submit in totality. If not, then representative sections of the tumor, at least one representative section per centimeter of tumor size (minimum of five sections) to include tumor with relationship to closest radial margin(s), tumor to normal and/or tumor to polyp interface, and tumor with relationship to adhered organs/structures (if applicable) should be submitted. When a mucinous tumor (or histologic evidence of a goblet cell adenocarcinoma) is present, it may be prudent to completely submit the entire lesion/appendix to fully evaluate the extent of disease.

2. Ileocolectomy/right colectomy

a. Using any orientation by the surgeon and/or orientation according to the peritoneal distribution, note and measure all portions of the intestine and any additional organs removed en bloc with the specimen.

b. Orient the specimen, distinguishing the serosa from the cut soft tissue. Note any serosal abnormalities including perforation, puckering, tumor implants, or exudate. Differentially ink the serosa and soft tissue margins in the area of the tumor(s).

c. If present, remove the staple line at proximal and distal intestine, cutting as close to the staple line as possible.

d. Open the intestine longitudinally.

e. Inspect the periappendiceal cecum.

f. Measure the tumor from the margins before fixation.

g. Provide gross intraoperative assessment or sample as needed for frozen section evaluation, if requested.

h. Pin and fix the specimen, generally overnight for proper fixation and to prevent shrinkage.

i. After fixation, re-ink the specimen if needed.

j. Sample margins (proximal and distal intestinal, mesenteric and/or vascular pedicle, and those of any adhered organ or structure). Margins far from the tumor may be representatively sampled, while closer margins should be sampled in totality. When sampling intestinal margins, the entire wall with mucosa and surrounding soft tissue should be represented in the sections.

k. Serially section the appendix and note tumor specifics as described in assessment of appendectomy specimen above.

l. Assess tumor relationship to any serosal findings or adhered organs.

m. If the tumor involves adjacent structures (cecum, ileocecal valve, ileum, or other organ or structure), describe involvement. If the tumor involves the nearby intestine, specifically note if the tumor extends through adhesions between serosalized tissue to secondarily invade the structures or if the tumor shows intramural spread.

n. Sample appendix and/or lesion/mass as described in assessment of appendectomy specimen above. See section VI for special considerations.

o. If tumor involves the appendiceal orifice, radial sections of the appendiceal orifice and periappendiceal cecum should be taken.

p. Examine the remainder of the specimen (including uninvolved areas of the intestines and other organs) and annotate any abnormalities.

q. Sample any other lesions in the intestine or adhered organ/structure.

r. Dissect lymph nodes and submit in totality except for grossly involved lymph nodes in patients that have not received neoadjuvant therapy. These lymph nodes can be representatively submitted. Lymph node

evaluation can be performed by manual methods or using fat-clearing agents. The methodology should be noted.

s. General recommendation for section submission for untreated tumors:

(1) Proximal intestinal margin, distal intestinal margin, and closest mesenteric and/or vascular pedicle margin as described above and margins from adhered organs/structures.

(2) Representative sections of the tumor to include tumor with relationship to serosa/any serosal lesions, tumor with relationship to closest radial margin (if applicable), tumor-to-normal and/or tumor-to-adenoma interface, tumor with relationship to appendiceal orifice/cecum (if applicable), and tumor with relationship to adhered organs/structures (if applicable).

(3) Representative sections of the any other abnormalities in the specimen.

(4) Representative sections of the uninvolved colon can be submitted but are not necessary.

(5) Sections of all possible lymph nodes.

VI. Special considerations

1. Mucinous tumors and pseudomyxoma peritonei

As the malignant potential for mucinous tumor previously described as "mucoceles" or "mucinous cystadenoma" is increasingly recognized, proper handling of these specimens is crucial for accurate diagnosis (Figure 9-3). Often the appendix is firm and enlarged with intraluminal mucin under pressure which can artifactually spill onto serosal surfaces or become pushed into tissue during sectioning. Thus, differential ink application and fixation before opening the specimen are helpful (if no intraoperative assessment is required). Features such as mucin in the wall, mucin/epithelial cells within periappendiceal soft tissue and on the serosa, perforation, mural fibrosis, and "pushing" invasion are important to recognize for proper designation and prognostication in these tumors; therefore, it is recommended that the majority of the lesion (if not all of the lesion) should be submitted for microscopic evaluation.

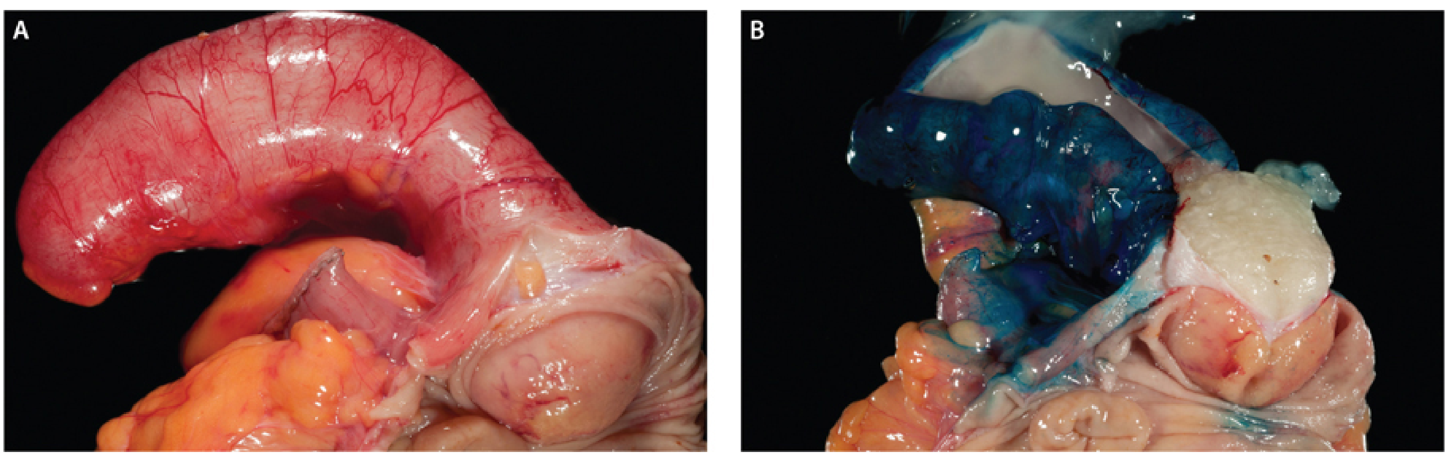

Figure 9-3. Low-grade appendiceal mucinous neoplasm (LAMN) involving appendix. A. The appendix is dilated and fluctuant to palpation. No serosal abnormalities are identified. The appendiceal orifice bulges into the cecal lumen. B. After inking the serosa, thin mucin extrudes from the appendiceal lumen.

In addition, if serosal-based mucinous implants are present on the terminal ileum and right colon, a right colectomy may be performed. Close inspection of the serosal surfaces of the ileum and colon is important, as these implants can be subtle with the appearance of fine erythematous serosal granularity. When additional specimens from cytoreductive procedures are received, they also should be inspected for these subtle lesions. In addition, larger serosal-based tumor implants can be seen, which in some cases not only involve the serosal surface but also push/invade into the organ proper (often intestinal resection or splenectomy specimens) or show predominantly parenchymal involvement (most commonly seen in ovaries). Histologic sections representing these findings are important. As the presence of neoplastic cells in intraabdominal sites (rather than acellular mucin) is a significant prognostic factor, proper sampling (both quantitative and qualitative) of mucinous

implants is important.[14] If the sample is small, submitting the entire tissue may be helpful. With thin peritonectomy specimens without significant implants, tissue rolls (such as those done for placental membranes) yield a large amount of surface area in limited cassettes. When choosing sections from mucinous implants, sampling fibrous areas rather than pure gelatinous areas may increase yield. In these specimens, margin assessment should be attempted (intestinal resections, abdominal wall resections) but is not always possible (such as on peritonectomies). Discussions regarding margin expectation on these specimens with the surgeon may be helpful, especially in patients not undergoing concurrent HIPEC.

2. Preoperative therapy

Neoadjuvant chemotherapy is generally not performed for appendiceal tumors except in the case of high-grade tumors, known metastatic disease, or increased tumor burden. Chemotherapy may decrease grade and tumor cellularity and increase extracellular mucin. Lymph nodes may be smaller, show involvement by fibrosis or mucin only, or be present in lower numbers after neoadjuvant chemotherapy.

Reporting of treatment effect is not designated in the CAP protocol for appendiceal carcinomas. If the patient has received neoadjuvant chemotherapy, the possibility of treatment effect should be noted and the stage of the tumor should be correctly annotated with the prefix, “y”.[8]

3. Adherent organs or structures

When adhered organs/structures are excised en bloc with the appendectomy/right colectomy specimen, histologic sections should be sampled in the areas of the adhesions between the tumor and the organ, as well as margins of the adhered organ/structure.

4. Postappendectomy specimens

As mentioned above, the tumor in an appendectomy specimen may only be identified upon microscopic evaluation. Depending on margin status, tumor type, and tumor stage, a more definitive resection to clear margins and/or properly stage the tumor (with evaluation of lymph nodes) may be necessary. In these cases, evaluation of the cecal base for the appendectomy site is generally performed, specifically noting and sampling residual intramural appendix/appendiceal stump, periappendiceal tumor deposits, and/or involvement of or residual tumor in the cecum. If no lesion/residual appendix is seen, radial sections of the entire appendiceal orifice/appendectomy site (after removal of any staples/sutures) is recommended.

VII. Example of grossing description of a right colectomy specimen removed for an appendiceal tumor

A. TERMINAL ILEUM, APPENDIX WITH TUMOR, RIGHT OVARY, RIGHT COLON – Received is a right hemicolectomy specimen consisting of the terminal ileum (6.0 cm in length and 3.5 cm in greatest circumference), cecum (9.0 x 7.0 x 1.0 cm), ascending colon (12.0 cm in length and 10.0 cm in circumference), and attached fluctuant appendix (7.5 cm in length and 4.0 cm in greatest diameter) with an ovary (3.4 x 1.1 x 0.9 cm) adhered to the tip of the appendix.

The serosa of the ileum, right colon, and mesentery shows fine erythematous granular lesions which are within 2.0 cm from the proximal ileal margin, 5.0 cm from the distal colonic margin, and 1.0 cm from the mesenteric margin. The appendix shows mucin protruding onto the serosal surface from a small defect in the wall located in the midportion of the appendix. Opening the lumen of the small intestine and colon reveals a bulging appendiceal orifice. Cross-sections of the appendix show a dilated lumen throughout the appendix filled with viscous mucin. The appendiceal wall is thin (approximately 0.1 cm) throughout. The abnormal appendix is 6.0 cm from the proximal margin, 15.0 cm from the distal colonic margin, 3.0 cm from the radial (retroperitoneal) soft tissue margin, and 9.1 cm from the mesenteric margin. The tip of the appendix is adhered to the ovary with a small amount of fibrous tissue (0.2 x 0.2 x 0.1 cm). In sectioning through the appendiceal tip and adhered ovary, no mucin or identifiable tumor is present in the adhesion or sections of the ovary.

No other lesions are identified in the mucosa of the ileum or colon. The ovary has two small simple cysts (0.1 and 0.2 cm). Twenty lymph node candidates are identified in the periintestinal soft tissue (0.3 to 0.5 cm in greatest dimension).

The intact and sectioned gross specimen is photographed. Representative tissue from the tumor and normal-appearing colonic mucosa are submitted for tissue banking under protocol.

Ink code: Blue-serosal surface of the appendix, ileum, and colon; orange-appendiceal defect, black retroperitoneal margin of ascending colon.

Section code

A1:Representative proximal ileal margin, en face

A2: Representative distal colonic margin, en face

A3: Mesenteric margin closest to serosal lesion, en face

A4: Retroperitoneal margin closest to appendiceal lesion, en face

A5-A6: Longitudinal sections of the appendiceal tip with adhered ovary

A7-A18: Remainder of appendix from proximal to distal aspect with defect in A18, cross-sections

A19-A21: Entire appendiceal orifice, radial sections

A22-A23: Sections of ileum with serosal lesions

A24-A25: Sections of colon with serosal lesions

A26-A27: Sections of mesentery with serosal lesions

A28-A30: Remainder of ovary with cysts in A28 and A29

A31-A33: Four whole lymph node candidates, each cassette

A34-A37: One bisected lymph node candidate, each cassette

VIII. Common potential staging pitfalls and solutions

Staging criteria differ slightly for carcinomas and neuroendocrine tumors. While both require knowledge of depth of invasion, neuroendocrine tumors at low T stage also need tumor size for categorization. Tumors in carcinoma group include adenocarcinoma “in-situ”/intramucosal adenocarcinomas (ie, invasion into lamina propria and muscularis mucosae but no submucosal invasion), adenocarcinoma and its variants (mucinous carcinoma, signet-ring cell carcinoma, etc), goblet cell adenocarcinoma, low-grade appendiceal mucinous neoplasms (LAMN), high-grade appendiceal mucinous neoplasms (HAMN), adenosquamous carcinoma, poorly differentiated neuroendocrine carcinoma (small cell and large cell types), mixed adenocarcinoma-neuroendocrine carcinoma (MANEC)/mixed neuroendocrine-nonneuroendocrine tumor (MiNEN), and undifferentiated carcinoma. Metastatic carcinoma and carcinomas arising from Mullerian glands should be excluded. Tumors staged as neuroendocrine tumors include only the (well-differentiated) neuroendocrine tumors (whether low [G1], intermediate [G2], or high grade [G3]). The following discussion relates primarily to glandular and invasive epithelial tumors, but some of the information may also be applicable to neuroendocrine tumors.

T category:

Unfortunately, acute appendicitis is the presenting finding in many patients with primary appendiceal tumors. The appendectomy specimen may be inflamed, perforated, dilated, or fragmented. Although appendiceal tumors are rare, proper routine gross evaluation of the appendectomy specimen is helpful when tumors are identified incidentally. If possible, designation of tissue at the resected base of the appendix and description and/or differential inking of the serosa and radial margin (adhered soft tissue and/or mesoappendix) may be advantageous during microscopic evaluation and when submitting additional sections. Because of the nature of tumors and the fact that gross features of appendiceal tumors are difficult to evaluate, often the entire appendix will need to be evaluated and submitted for microscopic evaluation. If tumors are evident (radiologically or grossly), sectioning and submission should be based on the gross findings rather than “routine sections” (eg, if a mucinous tumor involves the distal aspect of the appendix, sections will likely be more informative if the appendiceal tip is submitted as cross-sections rather than the routine longitudinal section commonly submitted on nontumoral specimens). For frankly obvious mucinous (or radiographically evident) tumors, close evaluation of the serosal surface for delicate mucinous deposits and fixation of the specimen (sometimes intact) make diagnoses less challenging. Awareness of telescoping of the mucosa (artefactual flipping of mucosa to the outer surface of the appendix), incomplete cross-sections, and diverticula help in

interpreting lesions. Occasionally, tumors (carcinomas and neuroendocrine tumors) arising at the base of the appendix may be difficult to distinguish from extension of tumors from nearby structures (ie, cecum, ileocecal valve, or terminal ileum). Knowledge of any lesions in these areas (precursor or predominance of tumor) with proper sectioning (if right colectomy) is beneficial. Not uncommonly, secondary lesions/tumors may be encountered with complete submission of the appendix. Lastly, the appendix may be entirely obliterated by some tumors. Review of clinical history to confirm that there has been no appendectomy in the past and generous sampling assist in evaluation.

For lower stage adenocarcinomas ("adenocarcinoma in-situ"/intramucosal adenocarcinoma) and evaluation of serosal penetration, much of the discussion regarding staging pitfalls provided in chapter 10, "Colon and Rectum," is relative to appendiceal tumors, as a subset of appendiceal tumors are morphologically indistinguishable from colonic primaries. As in the colon, invasion of these tumors deep to the mucosa generally elicits a desmoplastic stromal response.

Most recently, staging criteria for appendiceal mucinous tumors has changed in attempt to capture the unique behaviors of some of the lesions. These lesions include (conventionally invasive/colonic-type) mucinous adenocarcinoma and LAMN/HAMN. Mucinous adenocarcinoma has a propensity for lymphohematogenous spread, and thus an oncologic right colectomy is warranted. LAMNs (and most HAMNs) more commonly shows coelomic spread with features of the clinical syndrome of pseudomyxoma peritonei such as peritoneal implants, omental caking, mucinous ascites, and, in woman, ovarian involvement. Completion right colectomy may or may not be appropriate for LAMN/HAMN depending on histologic and clinical features. LAMN confined to the appendix has the unique T category of Tis (LAMN). Tis, T1, and T2 can be used for both mucinous adenocarcinoma and HAMN. In addition, current staging for appendiceal tumors allows acellular mucin to carry the same weight as neoplastic cells for both the T and M categories. Although, both mucin and neoplastic cells carry the same weight, notation of true neoplastic cells outside of the appendix in LAMN/HAMN provides important prognostic information for the clinician. Pitfalls include carryover of mucin or cells when sectioning these tumors; application of ink to the serosa, proper fixation, and sectioning, and the finding of an associated stromal or mesothelial reaction help with this distinction. Unfortunately, the appendix containing a mucinous lesion may need to be completely embedded to confirm the diagnosis and exclude other lesions (serrated polyp, rare true mucoceles) and to properly stage the lesion.

N category:

As in the colorectum, challenges with nodal staging include isolated tumor cells within lymph nodes versus N1 disease and distinguishing extramural lymphovascular/perineural invasion from discontinuous tumor foci (N1c). Isolated tumor cells (ITCs) are defined as single tumor cells or small clusters of tumor cells measuring 0.2 mm or less. For carcinomas, ITCs in isolation are regarded as N0 disease. Additional step sections to exclude larger foci (and, thus, N1 disease) is recommended. In the presence of N1 disease, the number of lymph nodes containing ITCs should be mentioned in the report but not included in the involved lymph node count. Also, specifically for carcinomas, soft tissue tumor foci are described as a distinct focus of tumor in the pericolic/perirectal fat or in adjacent mesentery (mesocolic or rectal fat) within the lymph drainage area of the primary tumor, but without identifiable lymph node tissue or vascular structure.[6,8] These may represent a lymph node completely replaced by tumor, lymphovascular invasion, or perineural invasion. Guidelines regarding ITCs and tumor deposits for neuroendocrine tumors have not been specifically addressed in guidelines provided by the American Joint Committee on Cancer (AJCC) or the CAP.[7,8]

M category:

As with the T category, mucin and neoplastic cells are both evaluated for the M category, in addition to the type of spread (peritoneal or nonperitoneal based). Adequate sampling of extraappendiceal disease is an area of controversy, but there may be significant outcomes between patients with cellular and noncellular disease, so sampling should be generous enough to ensure representation of the lesion (especially in low-cellularity specimens) and to justify excision of the organ. Finally, grading of metastatic disease is a component of staging in the appendix. For nonmucinous tumors, grade is based on gland formation similar to colorectal adenocarcinomas. For mucinous tumors, grade is based on criteria proposed by Davison et al.[16] The grade in

disseminated disease may be different from the primary lesion (eg, tumor in the abdomen may be high grade [G3], but appendiceal tumor is a LAMN).

IX. Synoptic pathology reporting

The current CAP protocol requires the following parameters to be included in the final pathology report. Synoptic reporting is not required for biopsy, primary resection specimens with no residual cancer (eg, following neoadjuvant therapy), or cytologic specimens. For neuroendocrine tumors, synoptic reporting is not required for recurrent tumor.

1. Appendiceal carcinomas (including LAMN/HAMN, goblet cell adenocarcinoma, and high-grade neuroendocrine carcinoma)[6]

- Procedure: Appendectomy, appendectomy and right colectomy, other (specify)
- Tumor Size: Provide at least greatest dimension (centimeters)
- Histologic Type: Use WHO classification of epithelial tumors of the gastrointestinal tract or those delineated in AJCC 8th edition[8,3,5,15]
- Histologic Grade: G1: well differentiated, G2; moderately differentiated; G3: poorly differentiated; other (specify); GX: cannot be assessed, not applicable, (per WHO classification of epithelial tumors of the gastrointestinal tract); G4: undifferentiated[5,8]
- Tumor Extension: No evidence of primary tumor; tumor invades lamina propria or muscularis mucosae; submucosa; into but not through muscularis propria; acellular mucin invades subserosa or mesoappendix but does not extend to the serosal surface; acellular mucin invades the visceral peritoneum (serosa); tumor invades through the muscularis propria into the subserosa or mesoappendix but does not extend to the serosal surface; tumor invades the visceral peritoneum (serosa); tumor directly invades adjacent organs or structures (specify); cannot be assessed
- Margins: Specify assessed margins (may include proximal, mesenteric, others); specify involved margins or the distance of invasive carcinoma, high-grade dysplasia, appendiceal mucinous neoplasm (low grade or high grade), and acellular mucin from closest margin in mm or cm if all margins are uninvolved
- Lymphovascular Invasion: Not identified, present, cannot be determined
- Tumor Deposits: Not identified, present (if present, number of deposits or number cannot be determined with explanation), cannot be determined
- Regional Lymph Nodes: Note presence or absence of number lymph nodes submitted or found and number of involved lymph nodes
- Pathologic Stage Classification (pTNM): Staging should be assessed according to guidelines provided by the AJCC 8th edition.[8] Report only pertinent categories based on the available information when the report is issued; if applicable, TNM descriptors should be included (m [multiple primary tumors], r [recurrent], y [posttreatment])

Optional elements include:

- Tumor Site (proximal half [include assessment of base of appendix – involved, uninvolved, cannot be assessed], distal half, diffusely involving appendix, not otherwise specified, other [specify])
- Perineural Invasion: Not identified, present, cannot be determined
- Additional Pathologic Findings
- Ancillary Studies

2. Well-differentiated neuroendocrine tumors (includes G1, G2, and G3 tumors)[7]

- Procedure Appendectomy, right hemicolectomy, other (specify)
- Tumor Site: Proximal half of appendix, distal half of appendix, diffusely involves appendix, appendix, not otherwise specified, other (specify)
- Tumor Size: Provide at least greatest dimension (centimeters)
- Histologic Type and Grade: Well-differentiated neuroendocrine tumor G1, G2, G3, GX (grade cannot be assessed) other (specify), not applicable

- Mitotic Rate: <2, 2-20, or >20/2 mm^2 (specify mitoses per mm2), cannot be determined (with explanation), not applicable
- Ki-67 Labeling Index: <3%, 3% to 20%, >20% (specify Ki-67 percentage), cannot be determined (with explanation), not applicable
- Tumor Extension: No evidence of primary tumor, tumor invades the lamina propria, submucosa, muscularis propria, through the muscularis propria into subserosal/mesoappendiceal tissue without involvement of visceral peritoneum, perforates the visceral peritoneum (serosa) or directly invades other organs or adjacent structures (specify), cannot be assessed
- Margins: Specify assessed margins (may include proximal, distal, radial or mesenteric, others); specify involved margins or the distance of tumor from closest margin in mm or cm if all margins are uninvolved.
- Lymphovascular Invasion: Not identified, present, cannot be determined
- Regional Lymph Nodes: Note presence or absence of number lymph nodes submitted or found and number of involved lymph nodes
- Pathologic Stage Classification (pTNM): Staging should be assessed according to guidelines provided by the AJCC 8th edition.[8] Report only pertinent categories based on the available information when the report is issued; if applicable, TNM descriptors should be included (m [multiple primary tumors], r [recurrent], y [posttreatment])

Optional elements include:

- Perineural Invasion: Not identified, present, cannot be determined.
- Additional Pathologic Findings
- Comments

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10. Colon and Rectum

Melissa W. Taggart, MD

Introduction

Colorectal resection specimens are routinely encountered as colorectal adenocarcinoma represents the third most common carcinoma worldwide.[1,2] Most tumors (over 90%) in the colorectum are adenocarcinomas. The second most common neoplasms in the colon are neuroendocrine neoplasms.[1] Because staging and prognostic parameters depend heavily on adequately sampled specimens, proper gross evaluation is crucial. Although the advent of neoadjuvant chemoradiation therapy for rectal lesions can present some challenges, gross evaluation of the colorectum in uncomplicated specimens is usually straightforward with proper orientation.

The location and extent of the lesion with radiologic evaluation of the high-risk features (adjacent organ/structure involvement and metastases to lymph nodes and distant sites), evaluation for synchronous lesions and background colorectal abnormalities, and preservation of function determine the type of procedure, most often with the goal of cure and diminishment of recurrence.[3] Excisions include localized intraluminal resection of the lesion: (1) endoscopic mucosal resection/endoscopic submucosal dissection/polypectomy and (2) transanal excision (transanal endoscopic microsurgery [TEM] and transanal minimally invasive surgery [TAMIS])[4]; and more complex intraabdominal resections, which include regional lymph nodes such as (3) ileo-/right colectomy which may or may not be extended past the transverse colon, (4) left hemicolectomy, (5) segmental resections, (6) proctectomy (low-/ultra-low anterior resection and abdominoperineal resection), (7) pelvic exenteration, (8) subtotal colectomy, and (9) total proctocolectomy. Adherent organs may also be present, for which margins and involvement by tumor need documentation both in the gross description and histologically. In resection specimens, regional (and possibly nonregional) lymph nodes are included. Intraabdominal resections may be performed through a laparotomy or laparoscopically and may or may not be robotically assisted. Occasionally, only polypectomy sites remain, which may be difficult to locate. As colorectal adenocarcinomas occasionally arise in the context of polyposis syndromes and idiopathic inflammatory bowel disease, proper documentation of the findings in the remaining colorectum is of great importance (see Figure 10-1).

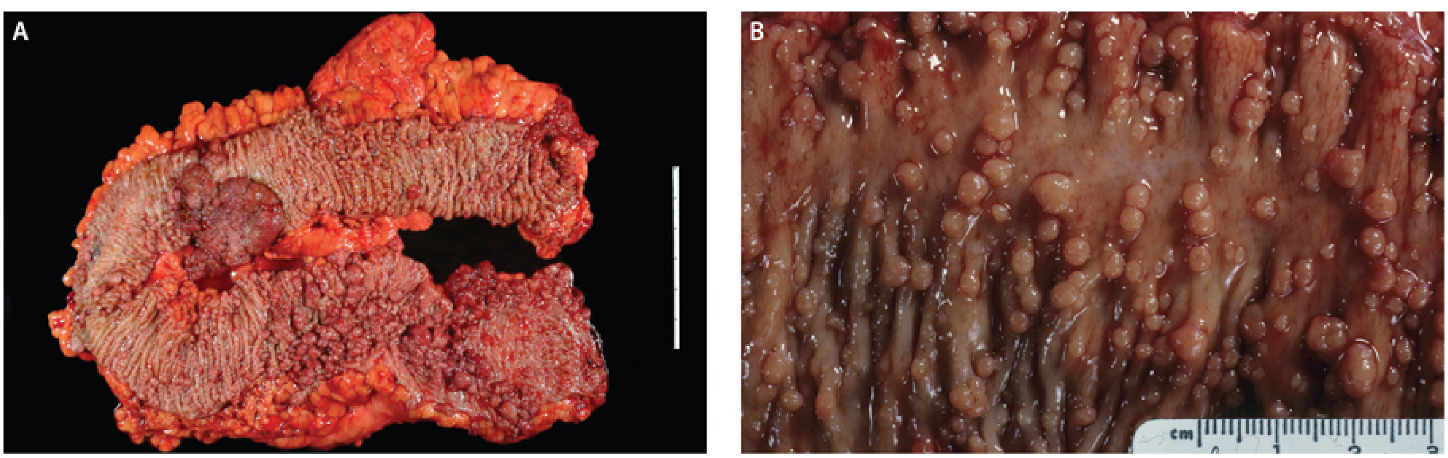

Figure 10-1. Familial adenomatous polyposis. A. A large adenocarcinoma is seen in the mid-portion of the specimen. B. Numerous small polyps are present throughout the colon.

The following represents recommendations for adequate gross and intraoperative assessment of colorectal specimens to provide an appropriate representation of the processes occurring in the specimen and sampling to provide information needed to fulfill College of American Pathologists (CAP) protocol requirements and direct subsequent treatment.[5]

I. Indications for different types of colorectal resections

Endoscopic features of a polypoid lesion in the colorectum (location, configuration [pedunculated, sessile, or flat], size, site, and features of invasive carcinoma [mucosal changes, focal depression, inability to lift]) will often determine whether polypectomy, endoscopic mucosal resection/endoscopic submucosal dissection, or deferral to a more invasive procedure is needed. Endoscopic mucosal resection in the colorectum requires the ability to lift the lesion after injection of saline (or other lifting agent) into the submucosa and thus is usually used for high-risk adenomas without invasion into the submucosa.[6] Transanal excisions provide transmural excisions of high-risk adenomas or early-stage carcinoma in the distal rectum. Occasionally, the excision extends deep to the muscularis propria, and sometimes one to a few lymph nodes may be sampled in the specimen.[7]

Right colectomies (ileocolectomy, right hemicolectomy) may be performed for ileal tumors (predominantly neuroendocrine tumors) and appendiceal tumors, as well as cecal, ascending, hepatic flexure, and proximal transverse colon tumors (Figure 10-2). Gross evaluation of right colectomy specimens for ileal and appendiceal tumors is included in their corresponding chapters. Left colectomies are performed for distal transverse, splenic flexure, descending, and proximal sigmoid colon tumors. Segmental resections are performed predominantly for mid-transverse and sigmoid colon cancers.

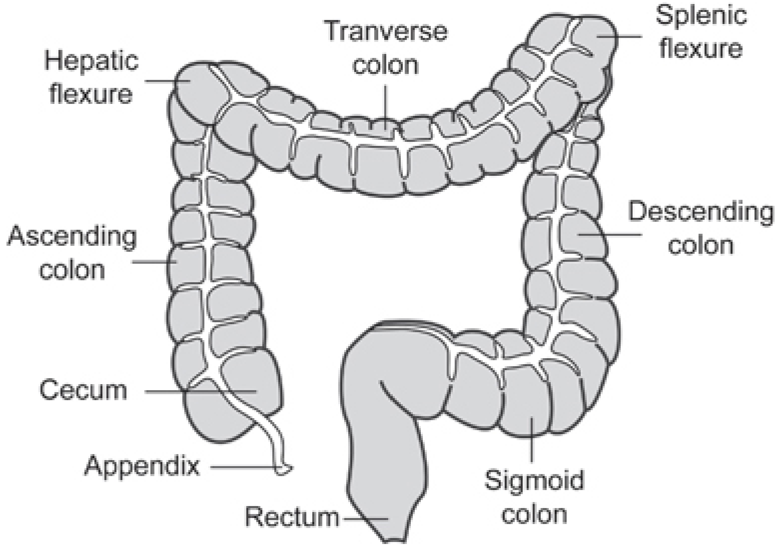

Figure 10-2. Anatomy of the colorectum. The right colon consists of the cecum and ascending colon, and the left colon consists of the descending and sigmoid colon.

Proctectomies are performed for distal sigmoid colonic, rectal tumors, and tumors of the anal canal (see corresponding chapter related to the gross evaluation of anal and perianal tumors for information related to these tumors), with the choice of the procedure for rectal tumors depending on the tumor site and ability to reasonably preserve sphincter function. Proctectomy specimens should include an intact total mesorectal excision, which includes the perirectal fat (mesorectum) excised along the mesorectal envelope (presacral [Waldeyer's] and pelvic parietal fascia) to decrease the risk of local recurrence.[3]

Localization of the tumor in proctectomy specimens may require gross evaluation (rectum begins at fusion of the sigmoid colon taenia coli) and clinical information (rectum ends at the beginning of the surgical anus, ie, distal large intestine at the anorectal ring, corresponding to the palpable proximal border of the puborectalis muscle on digital rectal examination). Tumors are considered as rectal if the inferior margin of the tumor is less than 16 cm from the anal verge or if any part of the tumor involves the intestine at least partially supplied by the superior rectal artery.[8] When rectal tumors involve other pelvic organs, a pelvic exenteration may be warranted.

Subtotal colectomy may be performed for polyposis syndromes if the density of polyps in the rectum is manageable by endoscopic surveillance. Otherwise, a total proctocolectomy may be required. In patients with ulcerative colitis of long standing or the development of flat dysplasia or carcinoma, a total proctocolectomy is

recommended; with a neorectum (ileal pouch anal anastomosis; J-pouch) being constructed from the ileum in most patients.

II. Specimen orientation, lesion identification, and evaluation of margins

Proper fixation allows for optimal sectioning of colorectal specimens; however, orientation of the specimen, evaluation of the integrity of the serosa (perforations, serosal defects, and serosal puckering), differential inking of visceral peritoneum and radial margins (all retroperitoneal, mesenteric, and pelvic soft tissue not covered by serosa that required excision to free the specimen), evaluation of the intestinal margins, and assessment of the mesorectal excision quality (for proctectomy specimens) should be performed in the fresh state (Table 10-1). Occasionally, portions of the parietal peritoneum, abdominal wall, or other adhered organs may be included with a specimen, and the relationship of the tumor to these areas along with margin assessment of the adhered organ/structure (if applicable) should be documented.

Table 10-1. Assessment of Mesorectal Excision Adequacy[9]

	Complete	Nearly complete	Incomplete
Mesorectum	Intact and smooth	Moderate bulk	Irregular, little bulk
Defects	<5 mm in depth	No visible muscularis propria*	Visible muscularis propria
Coning	None	Moderate	Moderate/marked
CRM	Smooth	Irregular	Irregular

* Except at insertion of the levator ani muscles.
CRM, circumferential resection margin.

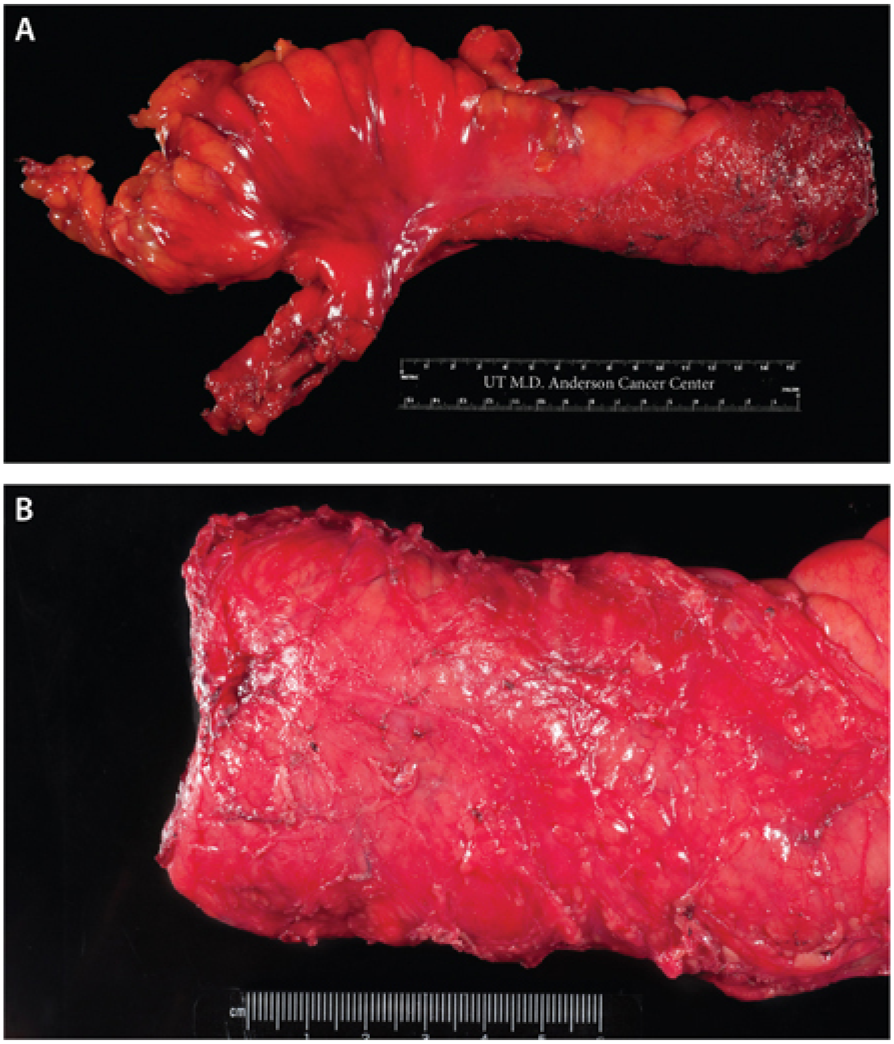

Figure 10-3. A. A low-anterior resection specimen performed for a rectal adenocarcinoma. B. A total mesorectal excision with adequate bulk and no coning or tears should accompany proctectomy specimens.

Localized resections may be submitted pinned on cork and may or may not be oriented. The transection edge/stalk margin of polypectomy specimens should be inked. Endoscopic mucosal resection and transanal excision specimens should be inked (differentially, if oriented) and submitted according to the orientation so that all peripheral and deep margins can be assessed. Occasionally, these specimens may be submitted by the surgeon in a piecemeal fashion, with or without further orientation. In these unoriented specimens, only peripheral tissue edges and deep margins can be assessed. The findings will need to be correlated clinically.

All intraabdominal resections should be oriented using the peritoneal surface, which may be challenging especially in the setting of inflammation, bulky tumor, and adhesions. If needed, the surgeon should assist in orienting the specimen and identifying the serosa and/or cut adventitia, as soft tissue not covered by a serosa should be considered a margin.

The only colonic specimens requiring orientation as to proximal and distal by the surgeon are sigmoid and transverse colectomies, as they are completely covered by serosa. The omentum may be still in its anatomic location, attached to the anterior aspect of the transverse colon. The cecum is reported to be completely covered by serosa (Figure 10-4A). In specimens with tumors in the cecum, transverse, or sigmoid colon, the only radial margin will be the transected mesenteric margin, and the "vascular tie" margin should also be assessed. Any other cut edge of the mesentery closer to the vascular tie should be separately assessed. The posterior aspects of the ascending and descending colon lie in the retroperitoneal fat and are not covered by serosa (Figure 10-4B). In these specimens, radial margins include the cut surfaces of the retroperitoneal adipose tissue and mesentery. The closest radial margin should be sampled, which in most cases is the retroperitoneal soft tissue. The rectum

has serosa on the anterior and lateral aspects in the upper third, serosa on the anterior aspect in the middle third, and no serosa on the distal third (completely surrounded by adventitia, "mesorectum"). The closest radial margin should be sampled, which in most cases is the pelvic soft tissue (Figure 10-4C). In proctectomy specimens for mid rectal tumors, radial margins include the cut surfaces of the retroperitoneal and pelvic soft tissue and mesentery (Figure 10-4C).

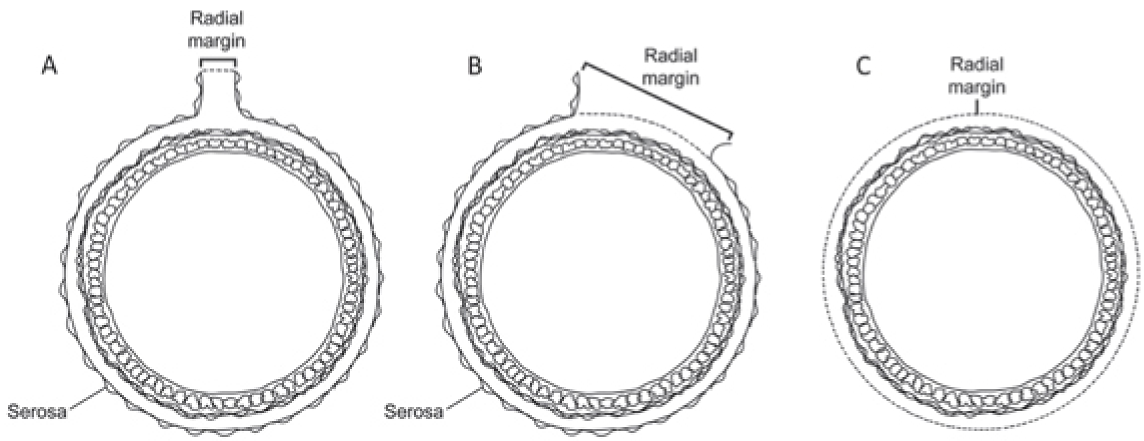

Figure 10-4. The serosa variably surrounds the colorectum, and the nonserosalized soft tissue is the considered the radial margin. In the transverse and sigmoid colon, the radial margin consists of the mesenteric cut surface (A). Figure B corresponds to areas of the colon that are only partially covered by serosa (ascending and descending colon and proximal and mid rectum). The entire distal rectum is surrounded by adventitia, which represents the radial margin (C).

Intraabdominal resections should be opened along the long axis before fixation, using manual palpation to direct the incision to the uninvolved wall of the specimen, if the tumor is not circumferential. Often intraoperative assessment consists of gross evaluation of the closest intestinal margin. Only rarely is frozen section assessment needed and is generally case specific. When assessing distal margins of proctectomy specimens if only a scar remains, palpation is helpful, and evaluation of the closest approach of palpated fibrosis to the margin may be prudent. After polypectomy or neoadjuvant therapy, the tumor bed may be difficult to identify. If present, knowledge of the placement of tattoo pigment from the endoscopic report (proximal, distal, at the lesion) is helpful.

The site of the tumor should be determined including the anatomic site of the tumor, laterality, and, for rectal tumors, position in relation to the anterior peritoneal reflection (eg, "tumor is on the anterior aspect of the proximal rectum entirely above the peritoneal reflection"; "tumor involves the posterior and medial aspect of the ascending colon"). If a tumor overlaps two sites, the subsite most involved is considered the primary site. If equally involved, the tumor can be registered as an "overlapping" lesion.[10] Before sectioning, the tumor size in two dimensions should be noted as well as the distance to the proximal and distal margin.[9]

After fixation, the tumor should be serially sectioned to determine the depth of invasion (measurement of the deepest aspect and estimation of the level of involvement) and evaluation of the closest radial margin. Other lesions in the nontumoral colorectum (diverticula, polyps, inflammatory changes, etc) should be noted.

IV. Tissue banking

Samples of fresh tumor, polyps, and/or normal mucosa can be performed according to institutional review board (IRB)-approved or patient-consented requests. Harvesting should be performed as soon as possible to decrease ischemic time. The protocol may require frozen section to confirm histology.

IV. Lymph node dissection

Identification of soft tissue deposits and involvement of lymph nodes by metastatic disease in the adventitia are crucial for determining stage and adjuvant therapy. After submission of relevant tumor sections, the remaining soft tissue can be dissected for lymph nodes. This is performed by the manual method (sectioning,

sight, and palpation) or by the use of fat-clearing reagents (graded alcohol solutions followed by xylene solution).[11] Fat-clearing solutions increase expense and toxicity to the prosector by use and disposal of solutions. In addition, effect on immunohistochemistry (if needed) is not completely known.[11,12] Studies have shown that the more lymph nodes identified, the better the prognosis; however, many factors (including preoperative therapy) can decrease lymph node yields.[13,14]

All lymph node candidates are submitted (grossly negative nodes in their entirety and, in the untreated tumor, grossly positive lymph nodes may be submitted representatively). The number of lymph nodes examined is associated with improved survival.[9,15] The American Joint Committee on Cancer (AJCC) recommends at least 12 lymph nodes be obtained in resection cases of untreated colorectal carcinomas; however, a pN0 designation may be assigned if fewer lymph nodes are obtained.[13,16,17] Pathologists should make every attempt to find all lymph nodes, and these attempts should be documented.[12,18] Larger lymph nodes should be serially sectioned.

Tumor deposits are an evolving concept in the 5th, 6th, 7th, and 8th editions of the AJCC staging manual and have been associated with decreased disease-free survival.[9,19-23] Currently, tumor deposits are defined as "discrete tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neuronal structure" and size and contour are no longer factors in the evaluation. These tumor deposits have been postulated to represent discontinuous spread of the tumor, venous invasion with extravascular spread or totally replaced lymph nodes.[24]

V. Grossing of colorectal specimens

1. Localized excisions

Localized resections may be submitted pinned on cork and may or may not be oriented.

Polypectomy:

a. The tissue should be measured and described, including tissue integrity, polyp configuration, and presence or absence of stalk.

b. The transection edge/stalk margin of polypectomy specimens should be inked.

c. The specimen is then sectioned, with the first section through the middle of the resection base/stalk if ample. If the base/stalk is narrow, a section slightly off center or to the side should be made. Tissue should be submitted on edge to this cut. If the sections need to be trimmed, they should be additionally sectioned or trimmed from the periphery and included for microscopic evaluation on edge to the cuts (Figure 10-5). The entire polyp should be submitted for processing.

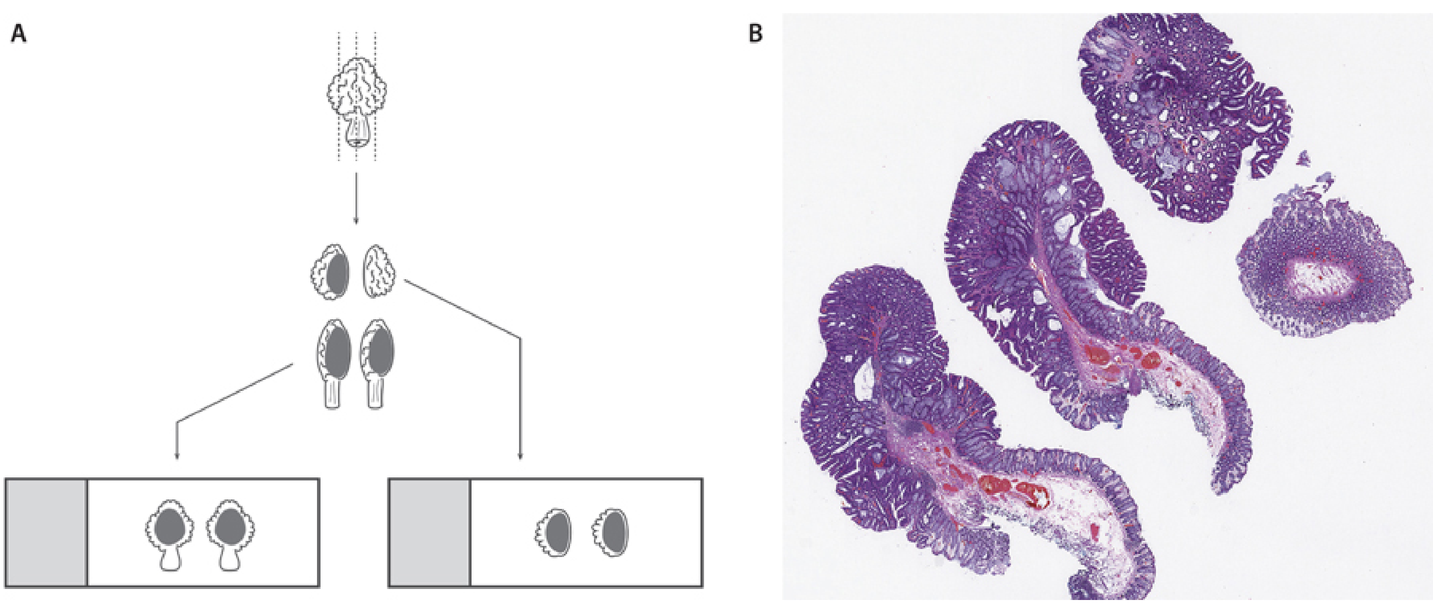

Figure 10-5. A and B. Example of sectioning and submission of a larger polyp. The first section should be made through the middle of the resection base/stalk if ample (or slightly off center or to the side if the base/stalk is narrow). Additional sections to the periphery of the polyp can be made and placed in separate cassettes.

2. Endoscopic mucosal resections/submucosal dissections/transanal excisions

a. The tissue should be measured and described, including tissue integrity, lesion details (lesion size and configuration, presence of ulceration), and distance to peripheral margins.

b. If oriented, the specimen should be differentially inked. Occasionally, these specimens may be submitted by the surgeon in a piecemeal fashion, with or without further orientation.

c. The tissue should be serially sectioned.

d. The lesion depth should be assessed qualitatively and quantitatively.

e. The tissue should be submitted according to the orientation so that all peripheral and deep margins can be evaluated, allowing for quantitative margin assessment. All tissue should be submitted for processing.

3. Intraabdominal resections

a. Using any orientation by the surgeon and/or orientation according to the peritoneal distribution, note and measure all portions of the intestine and any additional organs removed with the colon/colorectum.

b. Orient the specimen, distinguishing the serosa from the cut soft tissue. Note any serosal abnormalities including perforation, puckering, tumor implants, or exudate (Figure 10-6). If the specimen includes the rectum, assess the quality of the mesorectal excision (see Table 10-1). Differentially ink the serosa and soft tissue margins in the area of the tumor(s).

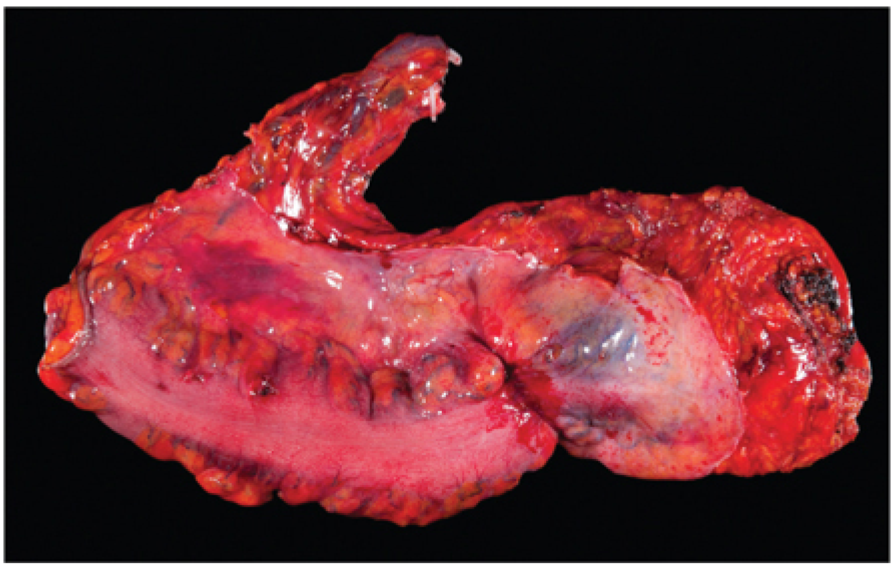

Figure 10-6. The serosa is puckered in this specimen, likely representing invasion of the tumor through the visceral peritoneum.

c. If present, remove the staple line at proximal and distal intestine, cutting as close to the staple line as possible.

d. Open the intestine longitudinally; using digital palpation to guide the cut onto the opposite side of the tumor if possible. If the tumor is circumferential, guide the incision away from any serosal lesions or adherent organs.

e. Visualize the lesion, measuring the tumor in two dimensions and noting the characteristics of the tumor (size, configuration [flat, sessile, polypoid, ulcerated]), amount of luminal involvement, and any adjacent/related lesion (adenoma, scar, tattoo pigment). Measure the tumor from the margins before fixation.

f. Assess tumor relationship to any serosal findings or adhered organs.

g. Provide gross intraoperative assessment or sample as needed for frozen section evaluation, if requested.

h. Examine the remainder of the specimen (including uninvolved areas of the intestines and other organs) and annotate any abnormalities.

i. Pin and fix the specimen, generally overnight for proper fixation and to prevent shrinkage.

j. After fixation, re-ink the specimen if needed.

k. Sample margins (proximal and distal intestinal, mesenteric and/or vascular pedicle, and those of any adhered organ or structure). If the tumor is less than 2 cm from a margin, then perpendicular sections showing the closest approach of the tumor to the margin is warranted (Figure 10-7). Otherwise, parallel/en face sections are adequate. Margins far from the tumor may be representatively sampled, while closer margins can be sampled in totality. When sampling intestinal margins, the entire wall with surrounding soft tissue should be represented in the sections.

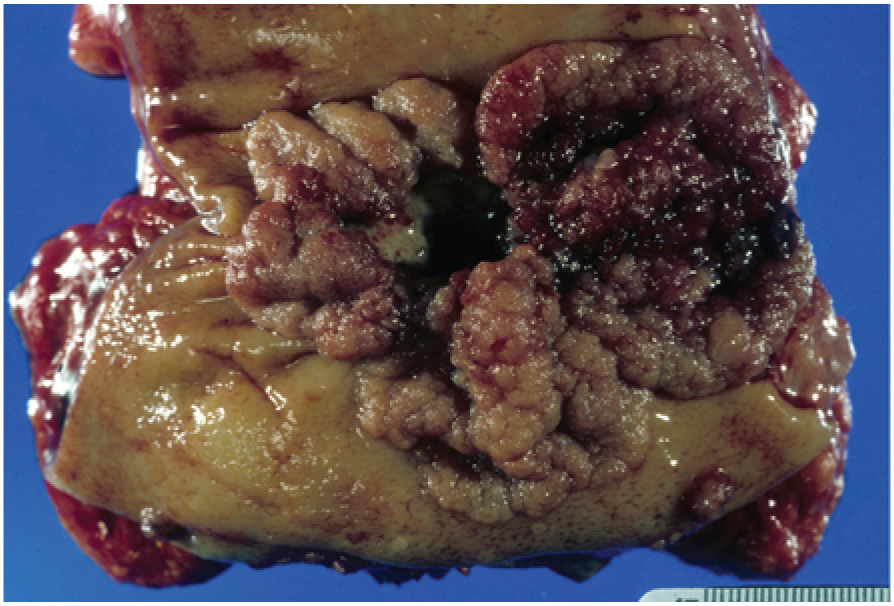

Figure 10-7. Since tumor is less than 2 cm from the distal margin, radial rather than en face margins allow accurate measurements of the tumor from the margin on microscopic sections.

(l) Serially section through the tumor to measure depth of the tumor and assess the relationship of the tumor to the serosa (and any serosal abnormalities), radial margin(s), and any adhered structures/organs

m. Sample the tumor, selecting and annotating sections to show deepest approach of the tumor to or involvement of the serosal surface and closest radial margin (closest radial margin will depend on tumor location in the intestine) and luminal involvement (eg, if an ascending colonic adenocarcinoma is present on the mesenteric side of the lumen, the closest radial margin may be the mesenteric margin rather than the retroperitoneal margin), tumor to normal or tumor to polyp interface, involvement (or lack of involvement) of adhered organs/structures (Figure 10-8). See section VI for special considerations.

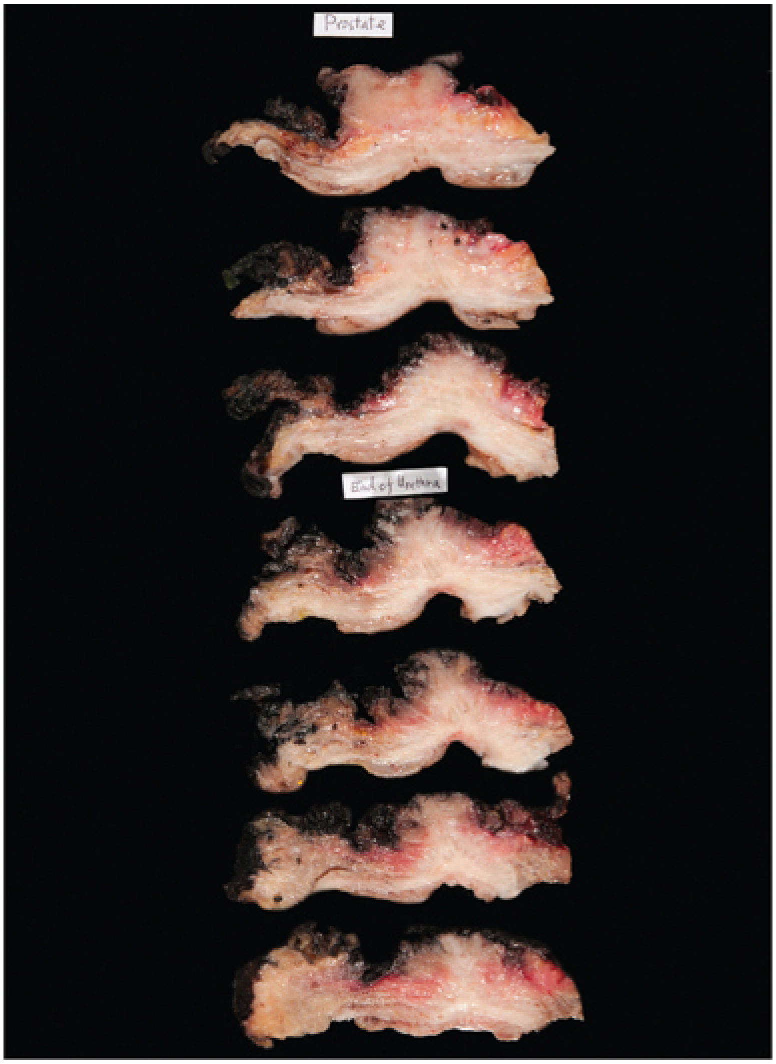

Figure 10-8. This treated tumor is blocked and serially sectioned, allowing for evaluation of the deepest invasion/fibrosis, involvement of adhered prostate and bladder, and evaluation of the distance of the tumor/fibrosis to the inked soft tissue.

n. Sample any other lesions in the intestine or adhered organ/structure.

o. Dissect lymph nodes and submit in totality. Grossly involved lymph nodes can be representatively submitted in specimens that have not received neoadjuvant therapy. Lymph node evaluation can be performed by manual methods or using fat-clearing agents. The methodology should be noted.

p. General recommendation for section submission for untreated tumors:

(1) Proximal intestinal margin, distal intestinal margin, and closest mesenteric and/or vascular pedicle margin as described above and margins from adhered organs/structures.

(2) Representative sections of the tumor, at least one representative section per centimeter of tumor size (minimum of five sections) to include tumor with relationship to serosa, tumor with relationship to closest radial margin, tumor to normal and/or tumor to adenoma interface, and tumor with relationship to adhered organs/structures (if applicable). Sections of "linear speculation" at the infiltrating edge increase the chance of finding large vessel invasion microscopically.25

(3) Representative sections of the any other abnormalities in the specimen.

(4) Representative sections of the uninvolved colon can be submitted but are not necessary.

(5) Sections of all possible lymph nodes.

VI. Special considerations

1. Resection for adenomas

If the resection is performed for an advanced adenoma (usually because of size and/or location), the adenoma should be submitted in its entirety as full-thickness sections. Villiform lesions may fragment while sectioning, and superficial fragments should be submitted in additional cassettes. Lymph node dissection should proceed as in a specimen containing a malignant lesion.

2. Resection after polypectomy for malignant polyp

Often only the polypectomy site will remain. Depending on the time interval between polypectomy and resection, a mucosal defect or a small scar (characterized by indentation or puckering of the mucosa) will remain. These areas may be difficult to identify, and details in the endoscopic report may be helpful. Endoscopic tattoo placement, when present, helps in localization; however, details of the relationship of the tattoo to the lesion (proximal, distal, proximal and distal, or within area of lesion) may be needed.

3. Neoadjuvant therapy

Preoperative therapy often decreases the size of the tumor, especially in the setting of chemoradiation therapy performed for rectal tumors.[26] Not uncommonly, the tumor is reduced to a small scar (Figure 10-9). Tattoo pigment may have been placed, and knowledge of the relationship of the tattoo to the tumor (proximal, distal, proximal and distal, or within area of lesion) may be vital. When evaluating gross distance of the tumor to the distal rectal margin, palpation of fibrosis may be helpful, with distance from the palpable fibrosis instead of the mucosal lesion used as the margin clearance. The distal rectal margin should be entirely submitted for microscopic evaluation for treated rectal tumors. Lymph nodes within the tumor bed should be submitted with sections of the tumor bed in a fashion to evaluate relationship of the lymph nodes to the mesorectal radial margin.[27]

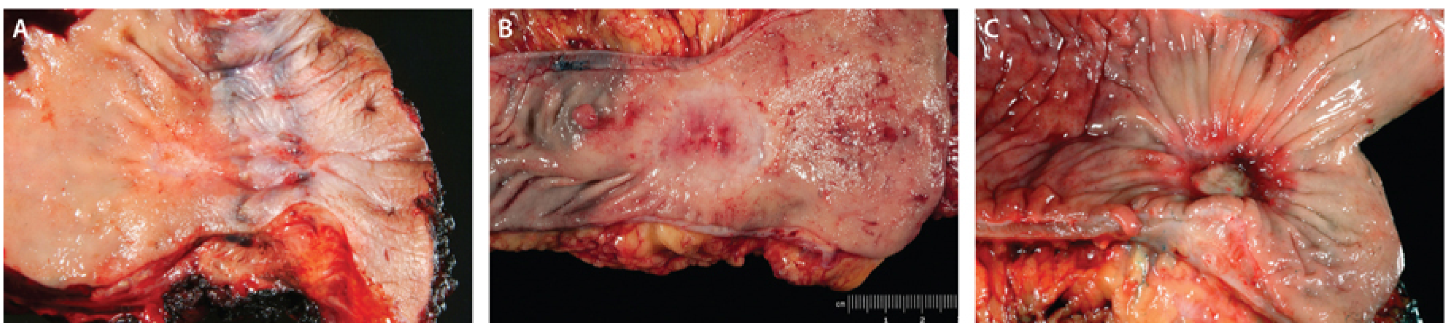

Figure 10-9. Neoadjuvant chemo(radiation) therapy can shrink tumor leaving scars (A), irregular mucosa (B), or an ulcer (C).

Gross tumor may not be evident and only fibrosis may be seen. If only fibrosis is identified upon serial sectioning, extensive sampling of the tumor bed is needed (with some institutions completely embedding the tumor bed) with preserved relationship of the fibrosis to the closest radial margin and/or serosa. If gross tumor remains, representative sections as described above may be submitted. Lymph nodes may be smaller or present in lower numbers after neoadjuvant chemotherapy.

4. Adherent or fistulized organs or structures/pelvic exenterations

When adhered organs/structures are excised en bloc with the colorectal specimen, histologic sections should be sampled in the areas of the adhesions/fistula between the tumor and the organ, as well as margins of the adhered organ/structure. In addition to the inclusion of pelvic organs, pelvic exenterations have abundant surrounding soft tissue, which often needs to be sampled thoroughly and with orientation as discerning treatment effect or inflammatory changes from tumor may be extremely difficult. When fibrotic, lymph nodes may be challenging to locate. In treated tumors, it may be prudent to submit lymph nodes that appear grossly involved by tumor in their entirety or develop a process for resampling if only treatment-related changes remain in the originally submitted sections.

5. Multiple tumors

Synchronous carcinomas can be present in certain patients. Proper sampling is needed to stage each tumor. In extended colectomies, regional lymph nodes should be separated and designated (as well as the dissected fibroadipose tissue, in the event additional evaluation is needed).

6. Polyposis syndromes

In polyposis syndromes, patients can have ten to thousands of polyps. A reasonable estimate of the number of polyps (count if less than 100) and notation of the distribution within the colorectum should be made. Any lesion with features suspicious for malignancy should be properly sampled, with the location noted and margin evaluation. Polyps over 1 cm should be sampled. Smaller polyps from the four quadrants of the colorectum should be sampled in at least one cassette per quadrant.[28] Proper sampling is needed to stage each tumor. In extended colectomies, regional lymph nodes should be separated (as well as the dissected fibroadipose tissue, in the event additional evaluation is needed).

7. Inflammatory bowel disease

The pattern and distribution of inflammatory lesions should be noted. Any raised or mass-forming lesion should be sampled. As in polyposis syndrome, multiple invasive tumors may be present, and proper sampling of the lesion (full thickness sections with serosal and radial margin relationship), as well as regional lymph node sampling, is needed.

VII. Example of grossing description of an intraabdominal colorectal specimen

A. TERMINAL ILEUM, APPENDIX, ASCENDING COLON WITH PORTION OF TRANSVERSE COLON AND ANTERIOR ABDOMINAL WALL – Received is an unoriented extended right colectomy specimen consisting of the terminal ileum (5 cm in length and 2 cm in diameter), appendix (6.2 cm in length and 0.5 cm in diameter), cecum (4.3 x 4.2 cm), ascending colon (12 cm length and 4.2 to 6.2 cm in diameter), and portion of transverse colon (6.2 cm in length 4.0 cm in diameter) with attached omentum (20 x 15 x 0.3 cm) with a portion of soft tissue (4.8 x 3.2 x 2.2 cm) adhered to the serosa of the ascending colon, representing a portion of anterior abdominal wall.

Opening the lumen of the intestine reveals a well-circumscribed circumferential mass (6.2 x 4.3 cm) in the ascending colon. The tumor is centrally ulcerated, and the periphery of the tumor shows heaped up borders. The lumen in the area of the tumor is stenotic but patent. Focally, the mucosa around the tumor is elevated and polypoid (1.0 x 0.8 cm area), suggestive of an adjacent polyp. The tumor is 10.2 cm from the proximal ileal margin, 7.1 cm from the distal transverse colon margin, and 8.2 cm from the closest mesenteric margin. Sectioning of the tumor shows a tan-white firm cut surface with foci of necrosis. The tumor measures 3.1 cm in depth. The tumor abuts and puckers the serosal surface. The tumor appears to invade the adhered soft tissue of the abdominal wall. The tumor invades through the colonic wall into the retroperitoneal soft tissue. The tumor is 0.4 cm from the closest retroperitoneal margin, 0.2 cm from the anterior/superficial aspect of the adhered abdominal wall, and 2.1 cm from the closest peripheral margins of the adhered abdominal wall.

No other lesions are identified on the serosal surface. There are two separate sessile polyps on the colonic mucosa. The first (1.2 x 0.8 x 0.1 cm) is present in the cecum, 6.2 cm from the tumor and 6.8 cm from the closest intestinal margin (ileum). The second (0.5 x 0.4 x 0.1 cm) is present in the transverse colon, 6.9 cm from the tumor and 1.2 cm from the closest intestinal margin (transverse colon). The mucosa of the ileum and remainder of the colon is unremarkable. Twenty-six lymph node candidates are identified with sectioning and palpation of the mesenteric and retroperitoneal soft tissue, ranging from 0.3 to 1.1. The largest lymph node appears grossly involved by tumor.

The intact and sectioned gross specimen is photographed. Representative tissue from the tumor and normal-appearing colonic mucosa are submitted for tissue banking under protocol (provide protocol number).

Ink code: Black-retroperitoneal margin, blue-serosa, orangeperiphery of the adhered abdominal wall, green-anterior/superficial aspect of the adhered abdominal wall

Section code

A1: Representative proximal ileal margin, en face

A2: Representative distal transverse colon margin, en face

A3: Mesenteric margin closest to tumor, en face

A4: Closest approach of peripheral margin of adhered abdominal wall to tumor, en face

A5: Tumor with closest approach to anterior/superficial aspect of adhered abdominal wall, perpendicular section

A6: Tumor with closest approach to retroperitoneal margin, perpendicular section

A7: Additional section of tumor to include adhesion between tumor and abdominal wall and abdominal wall

A8: Tumor with adjacent polypoid mucosa

A9: Tumor with adjacent normal mucosa

A10: Tumor with serosal puckering

A11-A13: Additional full thickness sections of tumor

A14: Cecal polyp in toto, serially sectioned

A15: Transverse colon polyp in toto

A16-A18: Five whole lymph node candidates in each cassette

A19-A21: Three whole lymph node candidates in each cassette

A22-A23: One serially sectioned lymph node in toto

A24: Representative sections of grossly involved lymph node

VIII. Common potential staging pitfalls and solutions

Staging criteria differ slightly for carcinomas and neuroendocrine tumors. While both require knowledge of depth of invasion, neuroendocrine tumors at low T stage also need tumor size for categorization. Tumors in carcinoma group include adenocarcinoma "in-situ"/intramucosal adenocarcinomas (ie, invasion into lamina propria and muscularis mucosae but no submucosal invasion), adenocarcinoma and its variants (medullary carcinoma, mucinous carcinoma, signet-ring cell carcinoma, etc), poorly differentiated neuroendocrine carcinoma (small cell and large cell types), squamous cell carcinoma, adenosquamous carcinoma, mixed adenocarcinoma-neuroendocrine carcinoma (MANEC)/mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN), and undifferentiated carcinoma. Metastatic carcinoma and carcinomas arising from Mullerian glands should be excluded. Tumors staged as neuroendocrine tumors include only the (well-differentiated) neuroendocrine tumors (whether low [G1], intermediate [G2], or high grade [G3]). The following discussion relates primarily to colorectal carcinoma but some of the information may also be applicable to colorectal neuroendocrine tumors.

T category:

Before a colorectal tumor can be properly staged, proper fixation and an appropriate gross examination is needed. Challenges include fragmentation of local excisional specimens (and occasionally intraabdominal resections), postpolypectomy resections, neoadjuvant therapy, and perforation and fistularization. Additionally, distal tumors in the anorectum may be require staging criteria for colorectum or anus, depending on site (may require knowledge of pretreatment location and clinical impression). As staging for tumors in the colorectum (both carcinoma and neuroendocrine tumors) require determination of the depth of invasion, orientation, and delineation of margins (peripheral and deep for endoscopic resections and proximal and distal intestinal/perianal skin and radial soft tissue, as well as additional margins when adhered tissue is resected, for intraabdominal resections). The serosa and resected soft tissue must be differentially inked, as well as any adhered tissue/organs. Adhered soft tissue (such as omentum, abdominal wall), serosal surface, and radial margins are difficult to distinguish from each other microscopically, and differing inks clarify and document these structures. According to the CAP, invasion of the external sphincter and/or levator ani muscle(s) should be classified as T4b.[10]

In lower stage tumors, invasion of the lamina propria ("adenocarcinoma in-situ"/intramucosal adenocarcinoma) can be challenging to distinguish from high-grade dysplasia (latter need not be staged). However, criteria for minimal invasion of the lamina propria is subjective and suffers from interobserver variability. Generally, the diagnosis of intramucosal adenocarcinoma can be made when changes in the degree of cytologic abnormalities (as compared to the surrounding adenoma) combined with the architectural

abnormalities exceed those of neoplasia confined to a normal crypt and features such as back to back glands with intervening stroma, small budding glands extending into the stroma, anastomosing glands, and solid growth pattern.[30] In polypectomy specimens in which the lesion is completely excised, intramucosal adenocarcinoma has virtually no capacity for metastasis and has been used synonymously with "high-grade dysplasia" in an attempt to prevent overtreatment of completely excised small tumors. Rarely, separate foci of tumor limited to the mucosa arising from a more extensively invasive adenocarcinoma elsewhere may be seen (intramural spread), which do not represent multiple tumors. If needed, molecular studies can confirm origin from the original tumor.

Invasion deep to the mucosa generally elicits a desmoplastic stromal response. In small biopsies and localized endoscopic resections, pitfalls can arise when there is mucosal displacement of dysplastic mucosa into the submucosa ("pseudoinvasion"). Features distinguishing pseudoinvasion from true invasion include lack of a desmoplastic stroma, rims of lamina propria surrounding glands, hemosiderin-laden macrophages, similar cytologic features between the mucosal and submucosal glands, and mucin pools without associated neoplastic glands.[31] Rarely, true invasion can be present in the background of pseudoinvasion, so careful evaluation is needed. Additionally, there can be dysplasia within glands of diverticula and extension of dysplastic glands into submucosal lymphoglandular complexes. Attention to the associated tissue generally reveals the true nature of the lesion.

Evaluating serosal invasion is a challenge. Currently, the recommendations by the CAP suggest that serosal invasion should be made on histologic findings rather than use of special stains. They offer the following guidelines for diagnosing T4a tumors: Tumor present at the serosal surface, free tumor cells on the serosal surface (on the visceral peritoneum) with underlying erosion/ulceration of mesothelial lining, mesothelial hyperplasia and/or inflammatory reaction, or perforation in which the tumor cells are continuous with the serosal surface through inflammation.[10] As stated previously, determination of the serosa from radial margins (such as the retroperitoneal surface of the ascending and descending colon and the mesorectum) require due diligence during gross examination, and differential inking of these two areas is extremely helpful in determining a positive radial margin from an advanced stage tumor.

Because the wide use of neoadjuvant therapy, tumors can be significantly reduced in size, with occasional lesions consisting only of a scar with no remaining viable tumor cells (pathologic complete response, pCR). pCR is a favorable prognostic factor and is generally only seen in lesions treated with chemoradiation therapy (ie, rectal tumors). When definitive tumor is not grossly visible, it is prudent to submit full sections of the entire tumor bed for microscopic evaluation. This allows quantification of tumor regression and measurement of the distance of tumor to the radial margin. It helps in the distinction between tumor deposits and discontinuous foci of treated tumor (T3 vs N1c disease), although additional step sections may also be required to make this distinction. Staging should be based on the depth of viable-appearing tumor cells and not therapy-related changes (such as fibrosis or acellular mucin pools). Finally, occasionally thickened muscularis mucosae and fatty tissue between the longitudinal and circular layers of the muscularis propria can present challenges in evaluating depth of invasion.

Neuroendocrine tumors in the colorectum usually arise near the ileocecal valve and rectum. When present in the ileocecal valve, evaluation (at least, gross evaluation) of the ileum is warranted, as some of these tumors may be better characterized as small intestinal primaries and staged as such. In addition, neuroendocrine tumors in the distal small intestine may be multiple.

N category:

The three largest challenges with nodal staging are adequate numbers of lymph nodes (especially in the setting of neoadjuvant setting), isolated tumor cells within lymph nodes vs N1 disease, and distinguishing extramural lymphovascular/perineural invasion from discontinuous tumor foci (N1c). At least 12 lymph nodes should be evaluated; however, the more lymph nodes evaluated help to determine the true nature of tumor and every attempt to finding all lymph nodes should be made. Neoadjuvant therapy can decrease the number and size of lymph nodes. If less than 12 lymph nodes are found, a statement describing additional attempts at lymph node retrieval should be made in the report. Again, only viable-appearing tumor cells indicate a positive lymph

node in the neoadjuvant setting. If therapy-related changes (fibrosis, necrosis, acellular mucin, etc) are seen in lymph nodes, then step sections to exclude small foci of tumor may be helpful in confirming node negative disease. In addition, when an extended segmental resection is performed, involvement of regional lymph nodes (N disease) should be distinguished from nonregional lymph nodes (M disease). Information regarding regional lymph nodes can be found in the *AJCC Cancer Staging Manual*.[9] Isolated tumor cells (ITCs) are defined as single tumor cells or small clusters of tumor cells measuring 0.2 mm or less. For carcinomas, ITCs in isolation are regarded as N0 disease, additional step sections to exclude larger foci (and thus N1 disease) is recommended. In the presence of N1 disease, the number of lymph nodes containing ITCs should be mentioned in the report but not included in the involved lymph node count. Although not definitively clarified, diminutive foci of tumor with therapy effect within lymph nodes after neoadjuvant therapy are best designated as N1 disease. Also, specifically for carcinomas, soft tissue tumor foci are described as a distinct focus of tumor in the pericolic/perirectal fat or in adjacent mesentery (mesocolic or rectal fat) within the lymph drainage area of the primary tumor, but without identifiable lymph node tissue or vascular structure.[9,10] These may represent a lymph node completely replaced by tumor, lymphovascular invasion, or perineural invasion. If the foci are within a large vessel or nerve or associated with lymphovascular remnants, they should be designated as lymphovascular or perineural invasion accordingly and not a soft tissue tumor focus. This determination can be made on routine hematoxyoin-eosin (H&E)-stained slides, utilize special stains (eg, histochemical stains for elastin or immunostains for endothelial cells), or step sections. In practice, ovoid foci near large arteries without a corresponding vein of similar size usually represent vascular invasion. Guidelines regarding ITCs and tumor deposits for neuroendocrine tumors have not been specifically addressed in guidelines provided by the *AJCC Cancer Staging Manual* or the CAP.[5,9]

IX. Synoptic pathology reporting

The current CAP protocol requires the following parameters to be included in the final pathology report. Synoptic reporting is not required for excisional biopsy (polypectomy), local excision (transanal disk excision), primary resection specimens with no residual cancer (eg, following neoadjuvant therapy), or cytologic specimens. For neuroendocrine tumors, synoptic reporting is not required for recurrent tumor.

1. Colorectal carcinomas (including high-grade neuroendocrine carcinoma)[10]

- Procedure: Right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoidectomy, low anterior resection, total abdominal colectomy, abdominoperineal resection, transanal disk excision (local excision), endoscopic mucosal resection, other (specify), not specified
- Tumor Site: Cecum, ileocecal valve, right (ascending) colon, hepatic flexure, transverse colon, splenic flexure, left (descending) colon, sigmoid colon, rectosigmoid region, rectum, colon, not otherwise specified, cannot be determined (explanation)
- Tumor Size: Provide at least greatest dimension (centimeters)
- Macroscopic Tumor Perforation: Not identified, present, cannot be determined
- Histologic Type: Use World Health Organization (WHO) classification of epithelial tumors of the gastrointestinal tract[32]
- Histologic Grade: G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; G4: undifferentiated; other (specify); GX: cannot be assessed, not applicable
- Tumor Extension: No evidence of primary tumor, no invasion (high-grade dysplasia), tumor invades lamina propria/muscularis mucosae (intramucosal carcinoma), submucosa, muscularis propria, through the muscularis propria into pericolorectal tissue, the visceral peritoneum (including tumor continuous with serosal surface through area of inflammation), or directly invades adjacent structures (specify); cannot be assessed
- Margins: Specify assessed margins (may include proximal, distal, radial or mesenteric, deep, mucosal, and others); specify involved margins or the distance of invasive carcinoma, intramucosal adenocarcinoma, high-grade dysplasia, and adenoma from closest margin in mm or cm if all margins are uninvolved (radial margins are considered involved if the invasive carcinoma is 0-1 mm from the margin)

- Treatment Effect: No known preoperative therapy; present (if present, optional scoring of treatment effect can be added using modified Ryan criteria)[10,32]
- Lymphovascular Invasion: Not identified, present (if present, optional reporting of the type of vessel and location can be included - small vessel lymphovascular or large vessel [venous] invasion [intramural or extramural]), cannot be determined
- Perineural Invasion: Not identified, present, cannot be determined
- Tumor Deposits: Not identified, present (if present, specify number of deposits or explanation or reason that deposits cannot be quantified)
- Regional Lymph Nodes: Note presence or absence of number lymph nodes submitted or found and number of involved lymph nodes
- Pathologic Stage Classification (pTNM): Staging should be assessed according to guidelines provided by the AJCC 8th edition.[9] Report only pertinent categories based on the available information when the report is issued; if applicable, TNM descriptors should be included (m [multiple primary tumors], r [recurrent], y [posttreatment])

Optional elements include:

- Tumor location (for rectal primaries): Entirely above the anterior peritoneal reflection, entirely below the anterior peritoneal reflection, straddles the anterior peritoneal reflection, not specified
- Macroscopic Intactness of Mesorectum (for rectal segmental resections): Complete, near complete, incomplete, cannot be determined
- Tumor Budding: Number of tumor buds in 1 "hotspot" field (specify total number in area=0.785 mm^2) (optional scoring can be performed: low score [0-4], intermediate score [5-9], high score [10 or more], cannot be determined)
- Type of Polyp in Which Invasive Carcinoma Arose: None identified, tubular adenoma, villous adenoma, tubulovillous adenoma, traditional serrated adenoma, sessile serrated adenoma/sessile serrated polyp, hamartomatous polyp, other (specify)
- Additional Pathologic Findings
- Ancillary Studies

2. Well-differentiated neuroendocrine tumors (includes G1, G2, and G3 tumors)[5]

- Procedure: Right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoidectomy, low anterior resection, total abdominal colectomy, abdominoperineal resection, transanal disk excision (local excision, endoscopic mucosal resection), other (specify), not specified
- Tumor Site: Cecum, ileocecal valve, right (ascending) colon, hepatic flexure, transverse colon, splenic flexure, left (descending) colon, sigmoid colon, rectosigmoid junction, rectum, colon, not otherwise specified, cannot be determined (explanation)
- Tumor Size: Provide at least greatest dimension (centimeters)
- Tumor Focality: Unifocal, multifocal (specify number of tumors), cannot be determined
- Histologic Type and Grade: Well-differentiated neuroendocrine tumor G1, G2, G3, GX (grade cannot be assessed), other (specify), not applicable
- Mitotic Rate: <2, 2-20, or >20/2 mm^2 (specify mitoses per mm^2), cannot be determined (with explanation), not applicable
- Ki-67 Labeling Index: <3%, 3% to 20%, >20% (specify Ki-67 percentage), cannot be determined (with explanation), not applicable
- Tumor Extension: No evidence of primary tumor, tumor invades the lamina propria, submucosa, muscularis propria, through the muscularis propria into subserosal tissue without penetration of overlying serosa, perforates the visceral peritoneum (serosa) or directly invades other organs or adjacent structures (specify), cannot be assessed
- Margins: Specify assessed margins (may include proximal, distal, radial or mesenteric, others); specify involved margins or the distance of tumor from closest margin in mm or cm if all margins are uninvolved
- Lymphovascular Invasion: Not identified, present, cannot be determined

- Regional Lymph Nodes: Note presence or absence of number lymph nodes submitted or found and number of involved lymph nodes
- Pathologic Stage Classification (pTNM): Staging should be assessed according to guidelines provided by the AJCC 8th edition.[9] Report only pertinent categories based on the available information when the report is issued; if applicable, TNM descriptors should be included (m [multiple primary tumors], r [recurrent], y [posttreatment])

Optional elements include:

- Perineural Invasion: Not identified, present, cannot be determined
- Additional Pathologic Findings
- Comments

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11. Distal Extrahepatic Bile Ducts

Wai Chin Foo, MD

Extrahepatic bile duct tumors include both proximal (or perihilar) and distal bile duct tumors. In the United States, the incidence of extrahepatic bile duct cancer has remained stable at between 0.95 and 1.02 per 100,000 cases over the last decade.[1] Distal bile duct tumors are defined as tumors whose epicenter lies between the cystic duct and common hepatic duct confluence and the ampulla of Vater and represent approximately 20% to 30% of extrahepatic bile duct tumors.[2] Like other biliary tree cancers, distal bile duct carcinomas are associated with primary sclerosing cholangitis, ulcerative colitis, choledochal cysts, and aberrant biliary tree anatomy.[3]

This chapter focuses on the appropriate handling of distal bile duct resections, which include both segmental resections and pancreaticoduodenectomies. The identification of surgical margins (including frozen section evaluation), gross examination, adequate sampling, and reporting of resection specimens using the College of American Pathologists (CAP) cancer protocol will be discussed.

The pathologist plays an important role in guiding subsequent therapeutic approaches after resection. Therefore, proper handling of the gross specimen, accurate histologic evaluation, and concise and meaningful reporting are critical.

I. Indications for resections

The common bile duct has an average caliber of 4.1 mm.[4] Because of the small diameter, even small tumors can result in obstructive signs and symptoms. In a large retrospective study, bile duct resections for malignant neoplasms represented 37.4% of resections.[5] Because most tumors involve the intrapancreatic bile duct, distal extrahepatic bile duct resections include both segmental resections and pancreaticoduodenectomies. Segmental resections are performed for tumors in the middle portion of the bile duct (ie, extrapancreatic) that do not involve the hepatic bifurcation or the pancreas. Pancreaticoduodenectomies are performed for tumors that involve the intrapancreatic bile duct.

II. What to expect grossly and microscopically

Bile duct carcinomas are thought to develop from either a mass-forming precursor (ie, intraductal papillary neoplasm of the bile duct [IPNB]) or a non–mass-forming precursor (ie, biliary intraepithelial neoplasia [BilIN; flat dysplasia]). IPNBs encompass tumors that were previously called papillomas, papillary adenomas, and papillary adenocarcinomas. Grossly, these precursors can be identified as sessile or polypoid intraductal growths. Microscopically, IPNBs can resemble intraductal papillary mucinous neoplasms (IPMNs) of the pancreas and are similarly characterized by atypical epithelial cells with pancreaticobiliary-type, intestinal-type, and gastric-type morphology. IPNBs can be further divided into low, intermediate, and high grades based on the degree of dysplasia. BilINs are characterized by atypical epithelial cells with multilayering of the nuclei and micropapillary architecture. BilINs are divided into BilIN-1 (low grade), BilIN-2 (intermediate grade), and BilIN-3 (high grade) on the basis of the degree of dysplasia. These lesions can also involve the peribiliary glands and can be misinterpreted as invasion. BilINs in the extrahepatic bile ducts resemble those found in the intrahepatic biliary tree.[3] Invasive carcinomas are irregular and infiltrative and can be associated with diffuse thickening of the duct wall.

III. Typical gross photographs of resections

Extrahepatic bile duct resections include both segmental (or local) resections and pancreaticoduodenectomies (see Figure 11-1). The mucosa of the bile duct can be granular and associated with abnormal fibrosis in the bile duct wall. In addition, the lumen can be dilated and/or contain an intraductal mass-forming precursor.

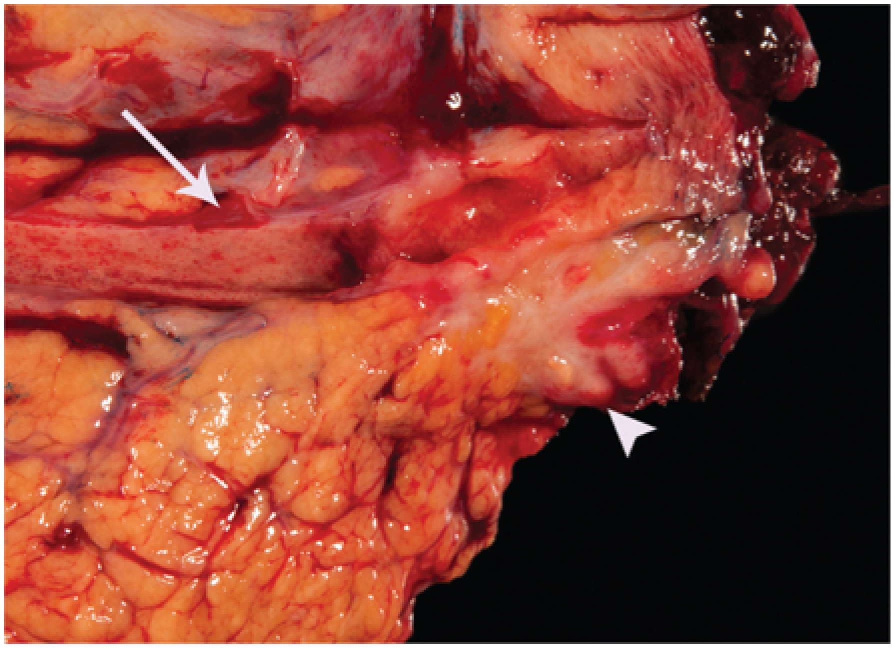

Figure 11-1. Pancreaticoduodenectomy specimen. There is an ill-defined tumor (arrowhead) in the common bile duct (arrow). Infiltration into the pancreas can be seen.

IV. Dissection techniques

Segmental resection

1. Orient the specimen, if possible, and ink the adventitia. The extrapancreatic bile duct can be difficult to orient because of the lack of distinct anatomy. Sutures placed by the surgeon may indicate the superior/proximal or the inferior/distal aspects.
2. Open the specimen longitudinally. If a palpable tumor is present, try to avoid cutting across the tumor.
3. If frozen section evaluation of the duct margins is requested, submit the margins en face.
4. Record the length, circumference, and wall thickness of the bile duct.
5. Record the size of the tumor, and describe the characteristics of the tumor.
6. Collect fresh tissue for tissue banks (if applicable) following institutional and protocol guidelines.
   a. A frozen section of the harvested tissue can be performed, if requested, in order to confirm the presence of tumor.
7. Pin the specimen and fix it overnight.
8. If the bile duct margins were not previously evaluated intraoperatively, submit the margins en face.
9. Section the tumor perpendicular to the longitudinal axis. Describe the depth of invasion, and record the distance of the deepest point of invasion to the adventitial margin. The tumor should be entirely submitted, and it is recommended that the bile duct be entirely submitted as well.

Pancreaticoduodenectomy

1. Orient the specimen and open the duodenum along the serosal side opposite the pancreatic head and the ampulla of Vater.
2. If frozen section evaluation of the pancreatic neck and bile duct margins is requested, submit the margins en face.
3. Insert probes in the main pancreatic duct and in the common bile duct. Be careful when probing the common bile duct and avoid dislodging a polypoid tumor in the bile duct.
4. Bisect the head of the pancreas and the common bile duct along the plane of the two probes; alternatively, the head of the pancreas and the common bile duct can be butterflied. Both methods allow visualization of the tumor's epicenter and its relationship to the ampulla of Vater, pancreas, and duodenum.
5. Record the size of the tumor, and describe the characteristics of the tumor.
6. Collect fresh tissue for tissue banks (if applicable) following institutional and protocol guidelines.

a. A frozen section of the harvested tissue can be performed, if requested, in order to confirm the presence of tumor.

7. Pin the specimen and fix it overnight.

8. Section the tumor perpendicular to the longitudinal axis. Describe the depth of invasion and involvement of adjacent structures (eg, duodenum and pancreas). The tumor should be entirely submitted, and it is recommended that the bile duct be entirely submitted as well.

V. Gross descriptions

The gross description provides context for the microscopic findings. As such, it is important to describe whether or not an intraductal mass-forming tumor is present. Invasive carcinomas that arise in IPNBs are associated with a higher median disease-specific survival after resection.[2] In addition, the location of the tumor and the relationship to the ampulla of Vater, main pancreatic duct, and duodenum should be included. By providing this information, the tumor can be staged accurately.

Segmental resection

Bile duct: A segment of bile duct (3 cm in length x 0.4 to 0.6 cm in diameter; 0.5 cm in wall thickness) that is dilated and oriented with a suture (per surgeon, proximal)

There is a bile-stained polypoid tumor (0.8 x 0.4 x 0.3 cm). No definitive invasion is identified, but the wall is thickened. The tumor is 1 cm from the proximal margin, 1.6 cm from the distal margin, and 0.2 cm from the adventitial margin. The tumor is entirely submitted.

The remainder of the bile duct mucosa is tan/white and granular.

Ink code: Black – adventitial

Section code

A1: Proximal margin, en face

A2: Distal margin, en face

A3-A5: Tumor and adventitial margin, in toto

A6: Bile duct proximal to tumor, representative

A7: Bile duct distal to tumor, representative

Pancreaticoduodenectomy

Pancreatic head, common bile duct, and duodenum: A pylorus-sparing pancreaticoduodenectomy consisting of the head of the pancreas (7.4 x 3.6 x 3 cm), a segment of the common bile duct (5 cm in length x 0.8 cm in diameter) with a metallic stent, and a segment of duodenum (15 cm in length x 5.5 cm in circumference)

There is an ill-defined, tan/white tumor (1.2 x 0.6 x 0.5 cm) in the common bile duct. The tumor involves both the extrapancreatic and intrapancreatic portions of the bile duct and invades 0.5 cm into the pancreas. No invasion into the duodenal wall is identified. No involvement of the ampulla of Vater is identified. The tumor is 1 cm from the common bile duct margin, 3 cm from the pancreatic neck margin, 3 cm from the uncinate (retroperitoneal) margin,[10] cm from the proximal duodenal margin, and 12 cm from the distal duodenal margin. The common bile duct mucosa is erythematous and granular, and the wall is thickened and fibrotic. A discrete intraductal mass is not identified. The tumor is entirely submitted.

The pancreas is unremarkable. There is congestion in the distal duodenum, but it is otherwise unremarkable. Twelve possible lymph nodes (ranging from 0.3 to 1.2 cm) are identified.

Ink code: Black – retroperitoneal margin

Section code

A1: Proximal duodenal margin, en face

A2: Distal duodenal margin, en face

A3-A4: Pancreatic neck margin, en face, in toto

A5: Common bile duct margin, en face

A6-A8: Retroperitoneal margin, perpendicular, in toto

A9: Tumor and pancreatic invasion

A10: Tumor and duodenal wall
A11: Remainder of tumor
A12: Common bile duct proximal to tumor, representative
A13: Common bile duct distal to tumor, representative
A14: Ampulla of Vater, radially sectioned, in toto
A15: Pancreas, representative
A16: Duodenum, representative
A17-A19: Possible lymph nodes, four in each block

VI. Common pathologic findings

Adenocarcinoma is the most common malignancy seen in these specimens (see Figure 11-2). The adenocarcinoma may be associated with an IPNB or BilIN (see Figure 11-3). However, a precursor may not be identified if the mucosa is completely denuded. Adenosquamous carcinoma and squamous cell carcinoma can also be seen and resemble their counterparts in the gallbladder (see Figure 11-4).

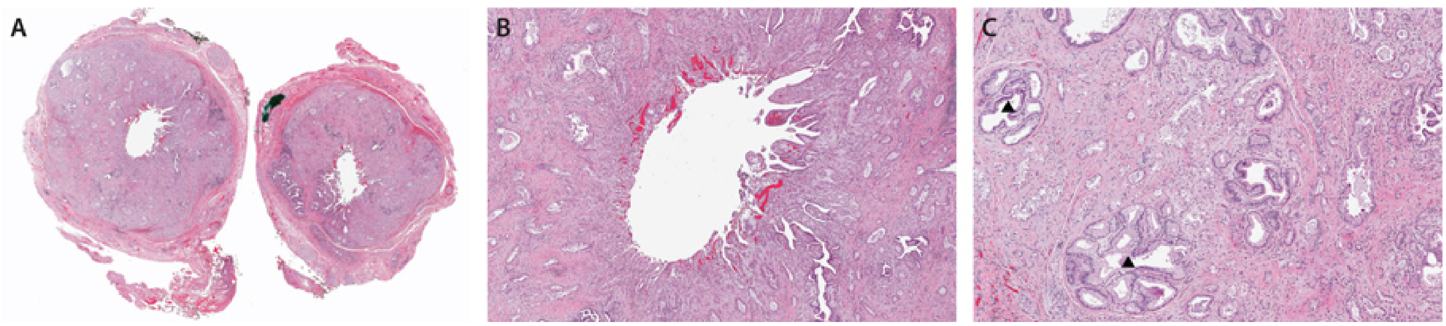

Figure 11-2. Adenocarcinoma. A. Adenocarcinoma with circumferential involvement of the common bile duct and invading beyond the wall of the bile duct. B. In this field, the adenocarcinoma shows biliary-type morphology, but subtyping is not required in the College of American Pathologists protocol.[6] The mucosa is largely denuded. C. The adenocarcinoma infiltrates around peribiliary glands (arrowheads).

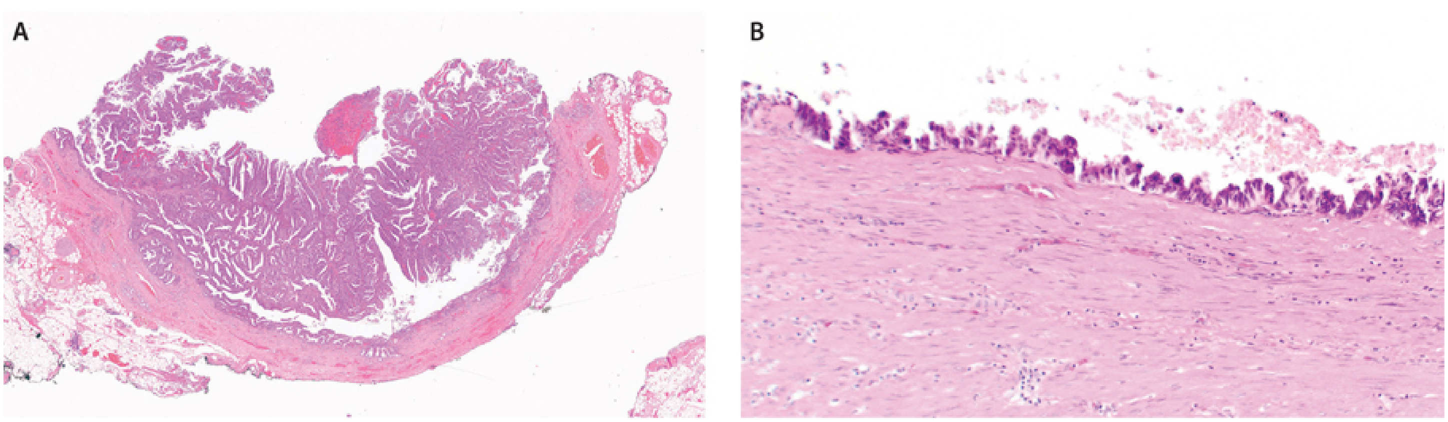

Figure 11-3. Precursor lesions. A. IPNB with intermediate grade dysplasia. No invasive carcinoma was identified in this tumor. B. BilIN-3 (high grade).

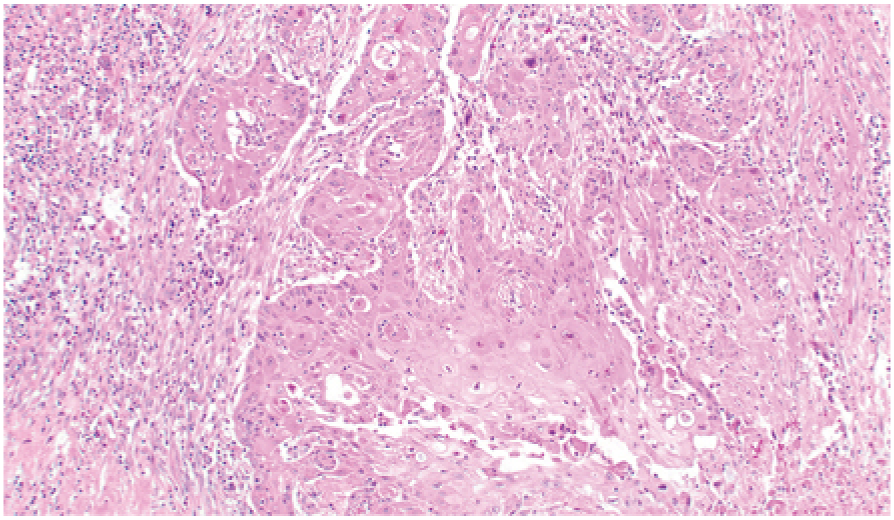

Figure 11-4. Squamous cell carcinoma. The tumor resembles its counterpart in the gallbladder and other sites.

VII. Common potential pitfalls and solutions

Most distal bile duct carcinomas involve the intrapancreatic portion of the common bile duct. These carcinomas can be difficult to distinguish from pancreatic carcinomas. Symmetrical growth around the bile duct and the presence of biliary intraepithelial neoplasia (or dysplasia) favor a bile duct origin.

VIII. What to include in the pathology report

At minimum, the report should contain the required elements in the CAP cancer protocol.[6] In the 8th edition of the American Joint Committee on Cancer's staging manual, the measurement of tumor invasion depth defines T1 to T3 categories.[2,6] This marks a departure from the use of the anatomic level of tumor invasion to define T1 to T3 categories. In addition to the required elements, the report should also convey information that may not be included in the cancer protocols and also provide clarification for problematic or complex diagnoses. Often, the "top-line diagnosis" can be used to elaborate on the summarized findings in the synoptic report. In addition, the synoptic report is, by definition, a summary of the entire case.

An example utilizing both the top-line diagnosis and the CAP cancer protocol for a segmental resection follows.

Final Diagnosis

(A) Common bile duct, segmental resection: Moderately differentiated adenocarcinoma (slide measurement, 0.3 cm) arising in an intraductal papillary neoplasm of the bile duct (IPNB) with low-grade dysplasia (0.8 cm). (See Synoptic Report/CAP protocol.)

All margins are negative for invasive carcinoma and high-grade intraepithelial neoplasia.

Synoptic Report

Procedure: Segmental resection of bile duct(s)

Tumor Site: Common bile duct

Tumor Size: Greatest dimension, 0.3 cm

Histologic Type: Adenocarcinoma, biliary type (extrahepatic cholangiocarcinoma)

Histologic Grade: G2: Moderately differentiated

Microscopic Tumor Extension: Tumor confined to the bile duct histologically

Depth of Tumor Extension: Tumor invades with a depth less than 5 mm

Margins: All margins are uninvolved by invasive carcinoma and high-grade intraepithelial neoplasia/dysplasia.

Margins examined: Proximal bile duct, distal bile duct, radial

Lymphovascular Invasion: Present

Perineural Invasion: Present

Regional Lymph Nodes: No nodes submitted or found

Pathologic Staging (pTNM):
TNM Descriptors: Not applicable
Primary Tumor (pT): pT1
Regional Lymph Nodes (pN): pNX
Distant Metastasis: Not applicable
Additional Pathologic Findings: Dysplasia

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12. Esophagus

Wai Chin Foo, MD

In the last several decades, the United States has witnessed an increased incidence of esophageal cancer. This trend is largely driven by the rising incidence of esophageal adenocarcinoma (EAC) and Barrett esophagus (BE), which only recently has stabilized.[1,2] EAC is the most common esophageal malignancy in the United States. In contrast, squamous cell carcinoma (SCC), the most common malignancy in the esophagus globally, has seen a decline in the United States and Western Europe over the last two decades.[3]

This chapter will focus on the appropriate handling of the most common esophageal specimens received by pathologists. These are specimens from endoscopic mucosal resection (EMR) and esophagectomy (or esophagogastrectomy) procedures. Given the survival benefits and widespread use of neoadjuvant therapy, assessment of specimens in these settings will also be covered. The identification of surgical margins (including frozen section evaluation), gross examination, adequate sampling, and the reporting of resection specimens using the College of American Pathologists (CAP) cancer protocol will be discussed.[4,5]

The pathologist plays an important role in guiding subsequent therapeutic approaches after resection. As such, proper handling of the gross specimen, accurate histologic evaluation, and concise and meaningful reporting is necessary.

I. Indications for endoscopic mucosal resection and esophagectomies

EAC and, to a lesser degree, SCC are the most common indications for EMRs and esophagectomies.[6] However, esophagectomies for melanoma and soft tissue neoplasms can also be encountered. Nonneoplastic conditions (eg, achalasia) may also prompt an esophagectomy. EMRs are limited surgical resections that can be used for both diagnoses, albeit rarely, and for curative intent, in other words, resection of high-grade dysplasia, intramucosal adenocarcinoma (pT1a), and superficially invasive adenocarcinoma (pT1b) without lymphovascular invasion and no nodal or distant metastases.[7,8] Esophagectomies for EAC and SCC, which include transhiatal and transthoracic approaches, are important for assessing the depth of invasion, nodal status, residual tumor burden, and margin status, which are important for determining prognosis.[9]

II. What to expect grossly and microscopically

In EMRs, the gross findings may vary from abnormal granular mucosa to an obvious tumor. In addition to those findings, an ulcerated, flattened, or depressed area—in other words, a treated tumor bed—can be seen in esophagectomies. Histologically, BE will be seen invariably in both EMRs and esophagectomies. Other histologic findings may include invasive carcinoma (EAC or SCC), residual carcinoma ranging from rare single cells to glands/sheets of cells, or fibrosis and hyalinization without residual disease. Comprehensive evaluation is critical for the assessment of prognosis and for guiding future therapies.

III. Typical gross photographs of endoscopic mucosal resections and esophagogastrectomies

Esophagogastrectomies will include a variable amount of stomach and can be oriented using the cardiac notch and the lesser omentum (see Figure 12-1) and can be performed for both neoplastic and nonneoplastic diseases (see Figure 12-2). Once opened, the gastroesophageal junction can be determined by identifying the end of the esophagus and the proximal aspect of the gastric folds. The relationship between the abnormality and the gastroesophageal junction may be important, eg, EAC.

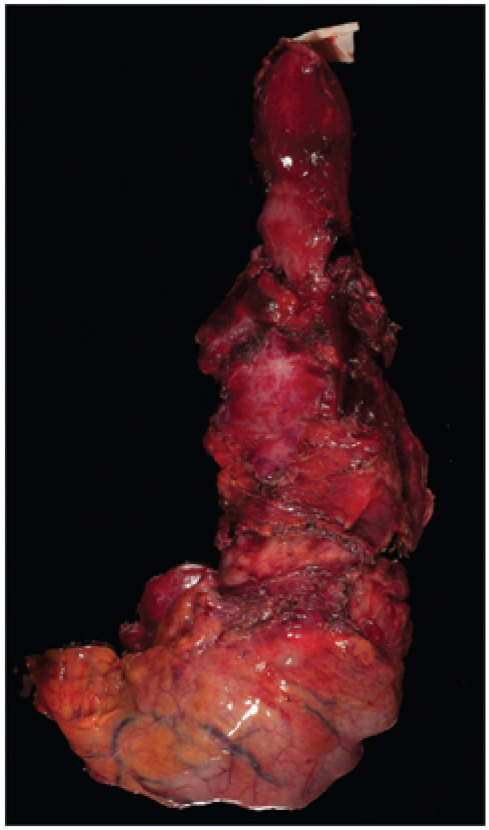

Figure 12-1. Esophagectomy (unopened) with esophagus and portion of stomach. Lesser omentum can be used to orient the anterior and posterior aspects of the specimen.

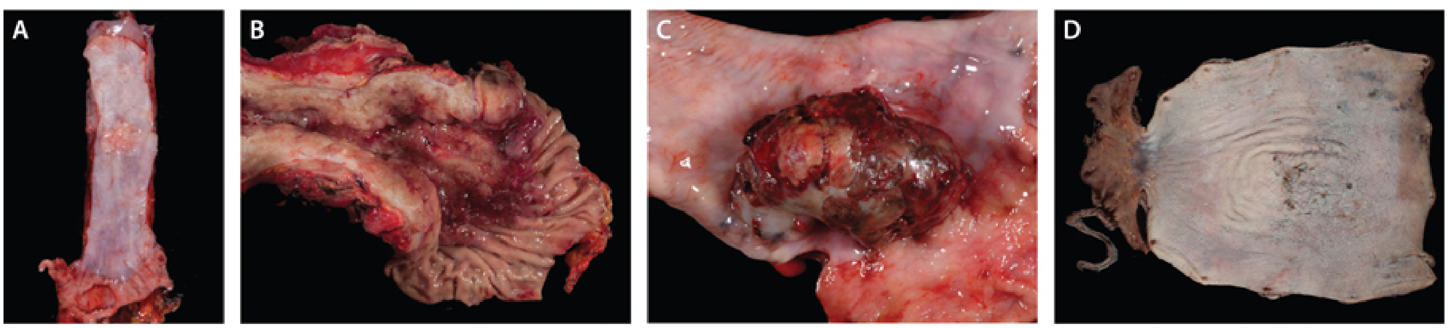

Figure 12-2. Esophagectomies for neoplastic and nonneoplastic issues. A. Squamous cell carcinoma in the midesophagus. B. Residual esophageal adenocarcinoma in the distal esophagus, gastroesophageal junction, and cardia. C. Melanoma in the gastroesophageal junction. D. Achalasia.

IV. Dissection techniques

Endoscopic mucosal resection

The endoscopic mucosal resection (EMR) specimen may be round or ovoid with a visible base. The EMR specimen may also be oriented with sutures, ink, and so forth. In addition, there may be a main specimen and other anatomically related specimens pinned on a rigid support, such as corkboard, to demonstrate the spatial relationship with each other. Photographs of the specimens are useful in order to assess the "true" mucosal margin in these multispecimen resections.

1. Orient the specimen (if applicable) and ink the peripheral and deep margins. If specific orientation is provided, differential inking should be used.
2. Pin the specimen and fix it for at least 12 hours. Overnight fixation is preferred.
3. Section the tumor at 0.2- to 0.3-cm intervals and entirely submit the specimen.

a. The two most peripheral sections away from the tumor (ie, tips) can be submitted en face. If the tumor is less than 0.1 cm, peripheral margins may be taken instead.

b. The remainder of the cross-sections can be submitted on edge.

Esophagogastrectomies

Esophagogastrectomies are for therapeutic resection of adenocarcinoma or SCC and for accurate staging, assessment of the resection margins, and to examine other features that also play a role in prognosis. In addition, in the neoadjuvant setting, evaluation of the residual tumor burden or tumor regression is important for prognosis.

1. Orient the specimen. The lesser curvature and greater curvature of the stomach can help in determining the anterior and posterior aspects of the stomach. The right side of the esophagus is continuous with the lesser curvature, and the left side of the esophagus and the greater curvature join at an acute angle called the cardiac notch.

2. Remove the staple line at the proximal and distal margins by carefully cutting as close to the staples as possible. Alternatively, the staples can be pulled out with forceps, but this is generally not recommended because it is time consuming and can tear the tissue.

3. Open the specimen longitudinally and avoid cutting across the tumor if possible. In posttreatment specimens, a palpable tumor may not be present.

4. Identify the gastroesophageal junction (GEJ). The GEJ is an anatomic site and is located at the end of the tubular esophagus where the proximal gastric folds begin. The Z-line (squamocolumnar junction) can be located at the GEJ. However, in Barrett esophagus, the Z-line may be irregular and located more proximally.

5. Identify the tumor or tumor bed in the postneoadjuvant therapy setting.

6. Identify the presence and extent of BE or squamous dysplasia (if applicable). BE is tan-pink and granular in comparison to normal squamous mucosa, which is smooth and tan-white. Squamous dysplasia may be harder to discern from normal squamous mucosa. Lugol's iodine can be used. It will highlight areas of normal mucosa, whereas the dysplastic epithelium will not pick up the dye.[10]

7. If a frozen section evaluation of the margin is requested, submit the proximal and distal margins.

a. If the tumor is greater than 1 cm from the margin, an en face section can be submitted.

b. If the tumor is less than 1 cm from the margin, a perpendicular section with the tumor and the margin (inked) is recommended.

c. The margin must be full thickness—in other words, it should include the mucosa, submucosa, and muscularis propria.

8. Record the length, circumference, and wall thickness of the esophagus and stomach.

9. Record the size and location of the tumor or tumor bed; describe the characteristics of the tumor (ulcerated, polypoid, etc) or tumor bed (ulcerated, fibrotic/scarred, etc). Describe the relationship of the lesion to the GEJ and record the distance of the tumor center to the GEJ.[4]

a. In postneoadjuvant therapy resection specimens, the tumor bed may be difficult to visualize. Treated tumor can appear ulcerated, depressed, fibrotic, and/or retracted. The location of the tumor should be correlated with previous pathology reports and/or endoscopy reports.

10. Collect fresh tissue for tissue banks (if applicable) following institutional and protocol guidelines.

a. A frozen section of the harvested tissue can be performed if requested in order to confirm the presence of tumor.

11. Ink the circumferential (or adventitial) margin underneath the tumor.

12. Fix the specimen overnight.

13. If the proximal and distal margins are not submitted separately or were not previously evaluated intraoperatively, submit the proximal and distal margins.

a. If the tumor is greater than 1 cm from the margin, an en face section can be submitted.

b. If the tumor is less than 1 cm from the margin, a perpendicular section with the tumor and the margin (inked) is recommended.

c. The margin must be full thickness—in other words, include the mucosa, submucosa, and muscularis propria.

14. Section the tumor or tumor bed parallel to the longitudinal axis. Describe the depth of invasion, and record the distance of the deepest point of invasion with the circumferential margin.

a. If this is a treatment-naïve resection specimen, submit representative sections of tumor (at least one per centimeter), including the deepest extent of invasion with the circumferential margin, the relationship to BE or squamous dysplasia, and the relationship to the stomach.

b. If this is a posttreatment resection specimen, submit the entire tumor bed, and include sections of the tumor with the adjacent esophagus and the stomach.

15. Describe the uninvolved mucosa in the esophagus and in the stomach.

16. Strip the adventitia from the esophagus, and dissect the soft tissue for regional lymph nodes. Lymph nodes are invariably present and may be close to the esophageal and gastric wall. Submit all the regional lymph nodes.

V. Gross descriptions

Endoscopic mucosal resection

Esophagus at 29-31 cm EMR: A mucosal resection specimen (2 x 1 x 0.7 cm) that is oriented by the surgeon (short stitch = 12 o'clock, long stitch = 3 o'clock)

There is a tan, ulcerated tumor (0.8 x 0.5 x 0.2 cm) that is 0.7 cm from the 12 o'clock margin, 0.5 cm from the 6 o'clock margin, 0.2 cm from the 3 and 6 o'clock margin, and 0.5 cm from the cauterized deep margin.

The specimen is entirely submitted.

Ink code

Blue: 12-3-6 o'clock margin

Orange: 6-9-12 o'clock margin

Black: deep margin

Section code

A1: 12 o'clock peripheral tip margin, en face

A2: 6 o'clock peripheral tip margin, en face

A3-A5:pecimen from 12 o'clock to 6 o'clock, in toto (A2-A4, tumor)

Treatment-naïve esophagogastrectomy

Esophagus and stomach, Ivor-Lewis esophagogastrectomy: An esophagogastrectomy specimen that includes a portion of esophagus (15 cm in length x 4 cm in circumference) and a portion of stomach (6 cm in length x 12 cm in circumference) with attached lesser curvature fat (4 x 3 x 1 cm).

There is a tan, firm tumor (3.5 x 3 x 2 cm) that is entirely located in the esophagus and does not involve the gastroesophageal junction (or located in the distal esophagus and involves the gastroesophageal junction; or centered at the gastroesophageal junction; or located in the proximal stomach or cardia and involves the gastroesophageal junction). The center of the tumor is 1 cm from the gastroesophageal junction. The tumor invades through the muscularis propria and into the periesophageal soft tissue. The tumor is 12 cm from the proximal margin, 6.5 cm from the distal margin, and 0.2 cm from the circumferential (adventitial) margin. The tumor is representatively submitted. The mucosa adjacent to the tumor is pink and extends to within 6 cm from the proximal margin.

The remainder of the esophagus is unremarkable. The stomach is unremarkable. Twelve lymph nodes (ranging from 0.2 to 0.8 cm in greatest dimension) are identified in the soft tissues.

Ink code: Black – circumferential (adventitial) margin

Section code

A1: Proximal margin, en face

A2: Closest distal margin, en face, representative

A3-A4: Tumor and deepest extent of invasion and circumferential margin

A5: Tumor and adjacent esophagus, representative
A6: Tumor and adjacent stomach, representative
A7: Abnormal esophageal mucosa and proximal margin, representative
A8-A11: Whole lymph nodes (four per block)

Postneoadjuvant therapy esophagogastrectomy

Esophagus and stomach, Ivor-Lewis esophagogastrectomy: An esophagogastrectomy specimen that includes a portion of esophagus (15 cm in length x 4 cm in circumference) and a portion of stomach (6 cm in length x 12 cm in circumference) with attached lesser curvature fat (4 x 3 x 1 cm)

There is an ulcerated, depressed, fibrotic tumor bed (3.5 x 3 x 2) that is entirely located in the esophagus and does not involve the gastroesophageal junction (or located in the distal esophagus and involves the gastroesophageal junction; or centered at the gastroesophageal junction; or located in the proximal stomach or cardia and involves the gastroesophageal junction.) The center of the tumor bed is 1 cm from the gastroesophageal junction. The fibrotic tumor bed obscures the muscular wall, and fibrotic tissue is seen in the periesophageal soft tissue. The tumor bed is 12 cm from the proximal margin, 6.5 cm from the distal margin, and 0.2 cm from the circumferential (adventitial) margin. The tumor bed is entirely submitted. The mucosa adjacent to the tumor is pink and extends to within 6 cm from the proximal margin.

The remainder of the esophagus is unremarkable. The stomach is unremarkable. Twelve lymph nodes (ranging from 0.2 to 0.8 cm in greatest dimension) are identified in the soft tissues.

Ink code: Black – circumferential (adventitial) margin

Section code

A1: Proximal margin, en face
A2: Closest distal margin, en face, representative
A3-A6: Tumor bed, in toto (A3-A4, tumor bed and deepest extent of invasion and circumferential margin; A5, tumor bed and adjacent esophagus; A6, tumor bed and adjacent stomach)
A7: Abnormal esophageal mucosa and proximal margin, representative
A8-A11: Whole lymph nodes (four per block)

VI. Common pathologic findings

The common pathologic findings in these specimens include BE, squamous dysplasia, intramucosal carcinoma, and invasive carcinoma (EAC and SCC). In addition, in posttreatment resections, a fibrotic tumor bed with and without residual disease can be seen. (See Figure 12-3.)

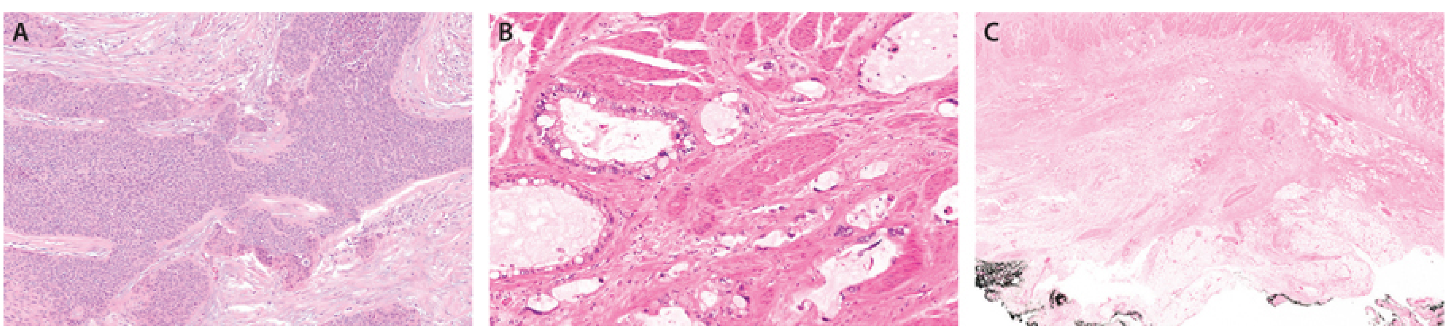

Figure 12-3. A. Squamous cell carcinoma. B. Esophageal adenocarcinoma with treatment effect. C. Ulcerated, fibrotic tumor bed extending into the adventitia.

VII. Common potential pitfalls and solutions

A common pitfall in EMRs and esophagectomies is incorrectly assessing the depth of invasion and, consequently, the pT stage because of alterations in the muscularis mucosae. The muscularis mucosae can be thinned, thickened, splayed, and duplicated in both resections for EAC and SCC (see Figure 12-4). Inaccurate pT staging resulting from abnormalities in the muscularis mucosae is more commonly seen in EMRs.[8,11] In the

postneoadjuvant setting, residual neoplastic disease can be difficult to recognize and may only be present as single neoplastic cells (see Figure 12-5). Immunohistochemistry can be useful in these settings.

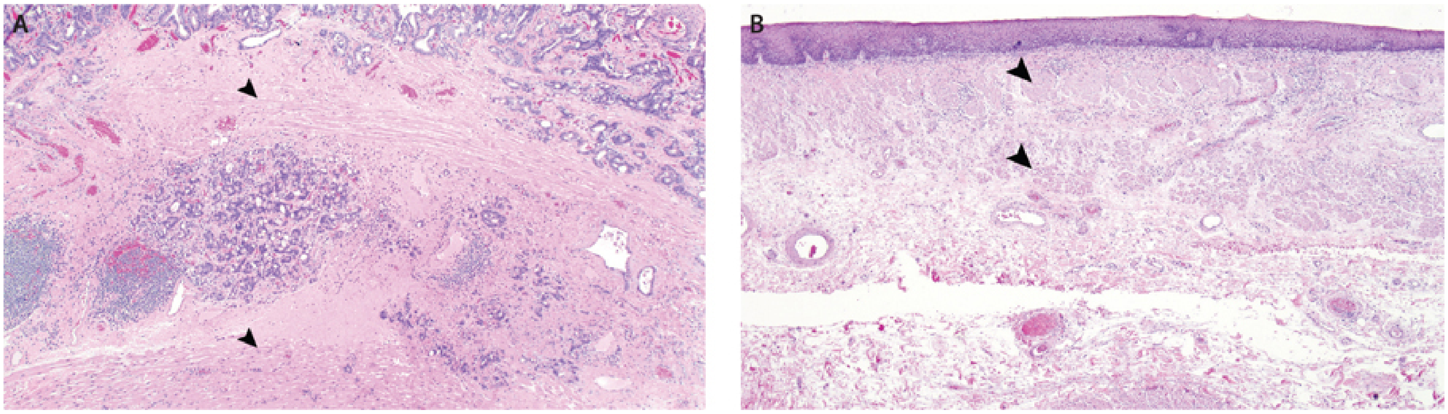

Figure 12-4. A. Endoscopic mucosal resection with adenocarcinoma between the splayed/duplicated muscularis mucosae (arrowheads). B. Esophagectomy with splayed/duplicated muscularis mucosae (arrowheads). This common pitfall is easily avoided because the muscularis propria is usually present for comparison.

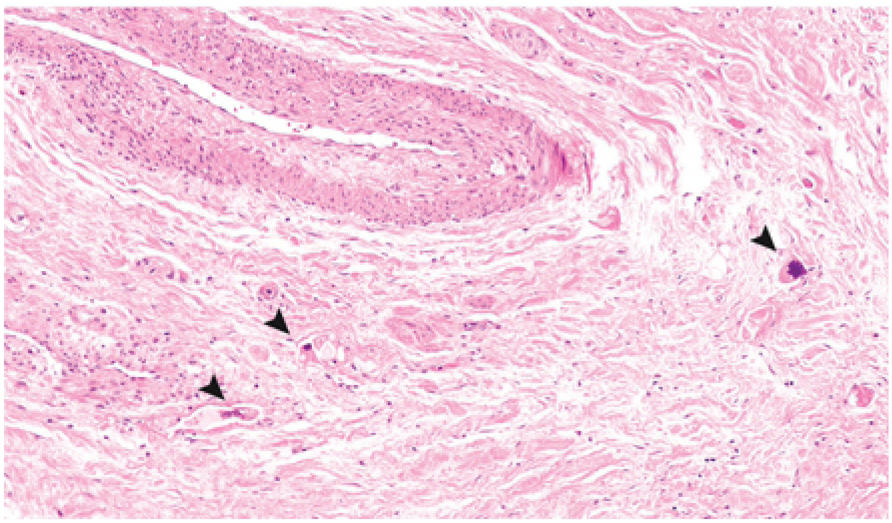

Figure 12-5. Single neoplastic cells representing residual adenocarcinoma (arrowheads).

VIII. What to include in the pathology report

At minimum, the report should contain the required elements in the CAP cancer protocol.[4,5] However, the report should also convey critical information that may not be included, as well as provide additional clarification for problematic or complex diagnoses. Often, the “top-line diagnosis” is used to elaborate on the summarized findings in the synoptic report. In addition, the synoptic report is, by definition, a summary of the entire case.

The specimens received and the procedure should be noted. Organs or structures that may be included in complex resections (eg, portion of diaphragm, pericardium, etc) should be included. The tumor site and size and the relationship of the tumor to the gastroesophageal junction, including the distance of the tumor center to the gastroesophageal junction (if applicable), should be provided in the gross description.

An example utilizing both the top-line diagnosis and the CAP cancer protocol for a posttreatment resection in which the pretreatment clinical TNM stage (cTNM) was cT3N24 follows.

Final Diagnosis

(A) Esophagus and stomach, Ivor-Lewis esophagogastrectomy:

Moderately differentiated adenocarcinoma (slide measurement, 0.2 cm) involving an ulcerated tumor bed (2.1 cm in greatest dimension) at the gastroesophageal junction (See Synoptic Report/CAP protocol.) Viable

tumor present in muscularis propria; fibrotic tumor bed extends into adventitial soft tissue.

All margins are negative for tumor.

Metastatic adenocarcinoma involves two of sixteen regional lymph nodes, including one node with treatment effect only (2/16).

(B) Lymph node, station 4R, lymphadenectomy: Four regional lymph nodes, negative for tumor (0/4)

(C) Lymph node, right axilla, lymphadenectomy: Metastatic adenocarcinoma with extranodal extension involves one of two lymph nodes (1/2).

Synoptic Report

Procedure: Esophagogastrectomy

Tumor Site: Distal esophagus (lower thoracic esophagus), esophagogastric junction (EGJ)

Relationship of Tumor to Esophagogastric Junction: Tumor midpoint lies in the distal esophagus and involves the esophagogastric junction

Tumor Size: Greatest dimension – 0.2 cm

Histologic Type: Adenocarcinoma

Histologic Grade: G2: Moderately differentiated

Microscopic Tumor Extension: Tumor invades muscularis propria

Margins: All margins are uninvolved by invasive carcinoma, dysplasia, and intestinal metaplasia

Margins examined: Proximal esophagus, distal stomach, and radial

Treatment Effect: Present, single or rare small groups of cancer cells (near complete response, score 1)

Lymph-Vascular Invasion: Not identified Perineural invasion: Present

Regional Lymph Nodes:

Number of Lymph Nodes Involved: 3

Number of Lymph Nodes Examined: 22

Pathologic Staging (pTNM):

TNM Descriptors: y

Primary Tumor (pT): pT2

Regional Lymph Nodes (pN): pN1 (including parts A and B)

Distant Metastasis: pM1 (including part C)

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13. Gallbladder

Wai Chin Foo, MD

Gallbladder cancer is an uncommon malignancy. In the United States, the incidence has risen from 0.9 cases per 100,000 to 1.13 cases per 100,000 in the last decade.[1,2] It is more commonly seen in certain populations in Mexico, Central and South America, India, Chile, and Japan, where it is a significant source of mortality.[2,3] Gallbladder cancer is associated with gallstones, primary sclerosing cholangitis, ulcerative colitis, choledochal cysts, and anomalous junctions of the pancreatic and common bile ducts.[2]

This chapter will focus on the appropriate handling of both simple and radical cholecystectomy specimens. The identification of surgical margins (including frozen section evaluation), gross examination, adequate sampling, and reporting of resection specimens using the College of American Pathologists (CAP) cancer protocol will be discussed.

The pathologist plays an important role in guiding subsequent therapeutic approaches after resection. As such, proper handling of the gross specimen, accurate histologic evaluation, and concise and meaningful reporting is necessary.

I. Indications for cholecystectomies

Cholecystectomies are most commonly performed for symptomatic cholelithiasis, asymptomatic cholelithiasis in patients with an increased risk of gallbladder cancer, and acalculous cholecystitis. It is also performed in patients who present with a gallbladder mass on imaging, eg, ultrasonography, computed tomography, and magnetic resonance imaging, without distant metastases, unreasonable regional nodal disease, or advanced involvement of critical vascular or biliary features.[4] In patients with incidental gallbladder cancer, observational studies have also reported improved survival in patients who undergo resection of the gallbladder bed for complete resection of any residual disease.[5]

II. What to expect grossly and microscopically

Gallbladder carcinomas are thought to develop from either a mass-forming precursor, eg, intracystic papillary neoplasm (ICPN), or a non–mass-forming precursor, ie, biliary intraepithelial neoplasia (BilIN; “flat dysplasia”). ICPNs encompass tumors that were previously called papillary adenoma and noninvasive papillary adenocarcinoma. Grossly, ICPNs are sessile or cauliflower-like lesions. Microscopically, ICPNs can resemble intraductal papillary neoplasms of the bile duct (IPNB) and are similarly characterized by atypical epithelial cells with pancreaticobiliary-type or intestinal-type morphology. ICPNs can be further stratified into low, intermediate, and high grade based on the degree of dysplasia. In contrast, BilINs are typically not identified grossly. However, the mucosa may be granular or plaque-like. BilINs are characterized by atypical epithelial cells with multilayering of the nuclei and flat or micropapillary architecture. BilINs are divided into BilIN-1 (low grade), BilIN-2 (intermediate grade), and BilIN-3 (high grade) based on the degree of dysplasia. Invasive carcinomas are irregular and infiltrative, and are frequently associated with diffuse thickening of the gallbladder wall.

Of note, gallstones are present in greater than 80% of gallbladders with carcinomas. Diffuse calcification of the gallbladder (porcelain gallbladder) can also be seen (present in up to 10% of the gallbladders with carcinoma.[2]

III. Typical gross photographs of cholecystectomies

Figures 13-1 to 13-3 demonstrate the typical gross pictures for different types of specimens and common lesions in the cholecystectomies. The gross appearance is mostly associated the microscopic morphology. A correlation is critical for the accuracy of the diagnosis and staging.

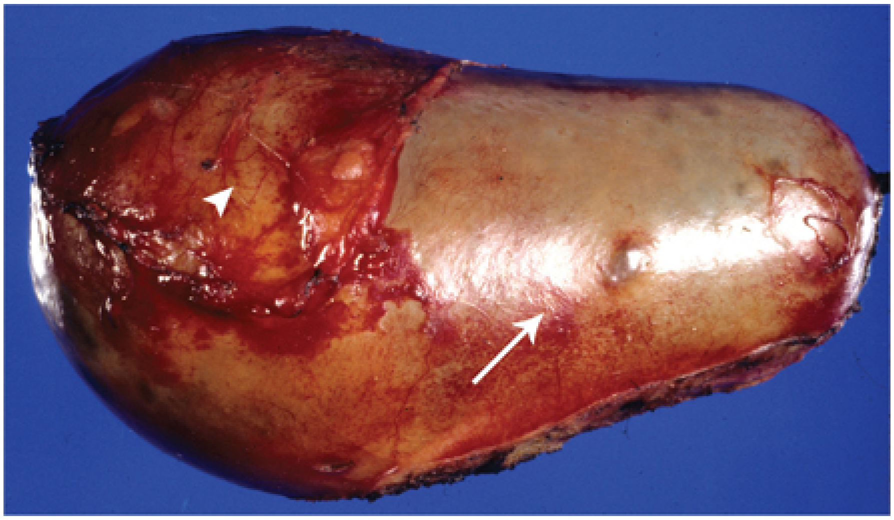

Figure 13-1. Simple cholecystectomy specimen. The gallbladder is distended. In contrast to the visceral peritoneum (arrow), which is smooth, the hepatic bed margin (arrowhead) is roughened.

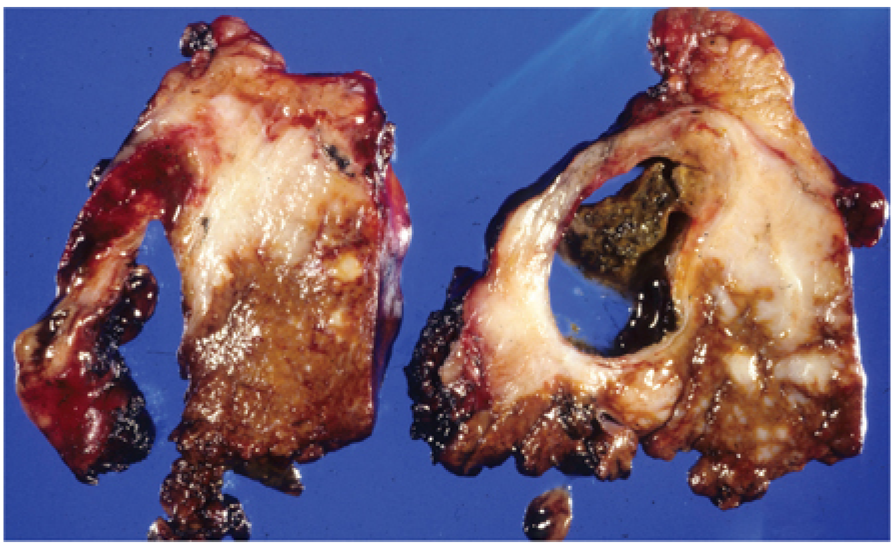

Figure 13-2. Radical cholecystectomy specimen. This cross-section demonstrates necrotic luminal debris and extensive tumor infiltration into the hepatic parenchyma. The tumor extends to the hepatic parenchymal margin (inked black).

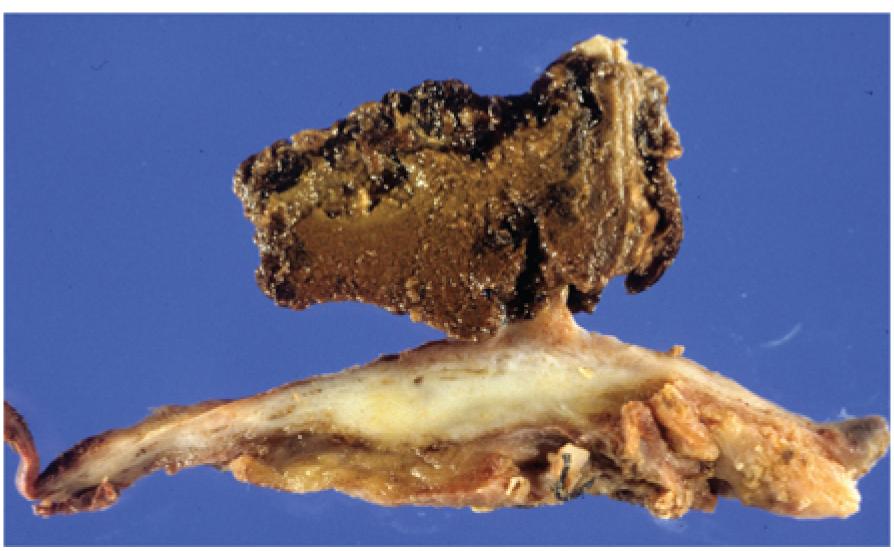

Figure 13-3. Simple cholecystectomy specimen. Although it is uncommon, this cross-section demonstrates metastatic disease (specifically, renal cell carcinoma) forming a polypoid mass in the gallbladder.

IV. Dissection techniques

Cholecystectomies (simple and radical)

1. Orient the specimen. The gallbladder is a saccular organ with visceral peritoneum on one side. The side of the gallbladder that is embedded in the liver lacks serosa.
2. Describe the serosa.
3. Open the specimen longitudinally from the fundus or the body to the neck or the cystic duct. If a mass-forming tumor is present, avoid cutting across the tumor if possible.
4. If a frozen section evaluation of the cystic duct margin is requested, submit the margin en face.
5. Examine and describe the mucosa and the luminal contents.
6. Record the length, circumference, and wall thickness of the gallbladder.
7. Record the size and location of the mass-forming tumor and describe the characteristics of the tumor. If a mass-forming tumor is not present, examine the wall of the gallbladder for abnormalities, eg, fibrosis.
8. Collect fresh tissue for tissue banks, if applicable, following institutional and protocol guidelines.
   a. A frozen section of the harvested tissue can be performed, if requested, to confirm the presence of tumor.
9. Ink the hepatic bed margin and serosa if a tumor or abnormalities in the wall are present. Differential inking should be used.
10. Fix the specimen overnight.
11. Submit the cystic duct margin en face if the margin was not previously evaluated intraoperatively.
12. If a mass-forming tumor is present, section the tumor parallel to the longitudinal axis. Describe the depth of invasion and record the distance of the deepest point of invasion with the hepatic bed margin.
    a. Polypoid tumors (or polyps) that are less than 1 cm are seldom neoplastic. The tumor should be entirely submitted; however, it is not necessary to submit the entire gallbladder.[4]
    b. Polypoid tumors (or polyps) that are greater than 1 cm often contain neoplasia.[4] The tumor should be entirely submitted. In addition, a complete microscopic evaluation of the gallbladder is recommended.[6]
13. If a mass-forming tumor is not present, representative sections from at least three random areas and the cystic duct margin should be submitted for microscopic evaluation. The presence of dysplasia or neoplasia from these sections should prompt complete sampling of the gallbladder.[4,6]

V. Gross descriptions

The gross description provides context for the microscopic findings. As such, it is important to describe the presence (or absence) of a mass-forming tumor. Invasive carcinomas that arise in mass-forming precursors, eg, ICPN, have the most favorable prognosis.[2,7] In addition, the location of the tumor on the hepatic side or the peritoneal side should be included. By providing this information, the tumor can be accurately staged.

Cholecystectomy (simple or radical)

GALLBLADDER – a gallbladder (6 cm in length x 1-4 cm in circumference; 1 cm in wall thickness) filled with viscous bile and containing five choleliths.

There is bile-stained polypoid tumor (2 x 3 x 2 cm) that is located in the body on the peritoneal side of the gallbladder. No invasion into the wall is identified, but the wall is thickened, including the wall on the hepatic side. The tumor is 3 cm from the cystic duct margin.

The remainder of the gallbladder mucosa is bile stained with flecks of yellow/green, gritty material.

INK CODE: Black – hepatic bed margin; blue – serosa.

SECTION CODE: A1, cystic duct margin, en face; A2, gallbladder and hepatic bed margin, perpendicular; A3 – A5, tumor and serosa; A6, tumor and adjacent gallbladder mucosa; A7, mucosa in the fundus, A8, mucosa in the body; A9, mucosa in the neck.

VI. Common pathologic findings

Adenocarcinoma is the most common malignancy seen in these specimens. The adenocarcinoma may be associated with an ICPN or BilIN. However, a precursor may not be identified if the mucosa is completely

denuded. Adenosquamous carcinoma and squamous cell carcinoma can also be seen, but the latter is far less common. Involvement of Rokitansky-Aschoff sinuses can also be seen. The following microscopic photos illustrate common entities for cholecystectomies (Figures 13-4 to Figure 13-6).

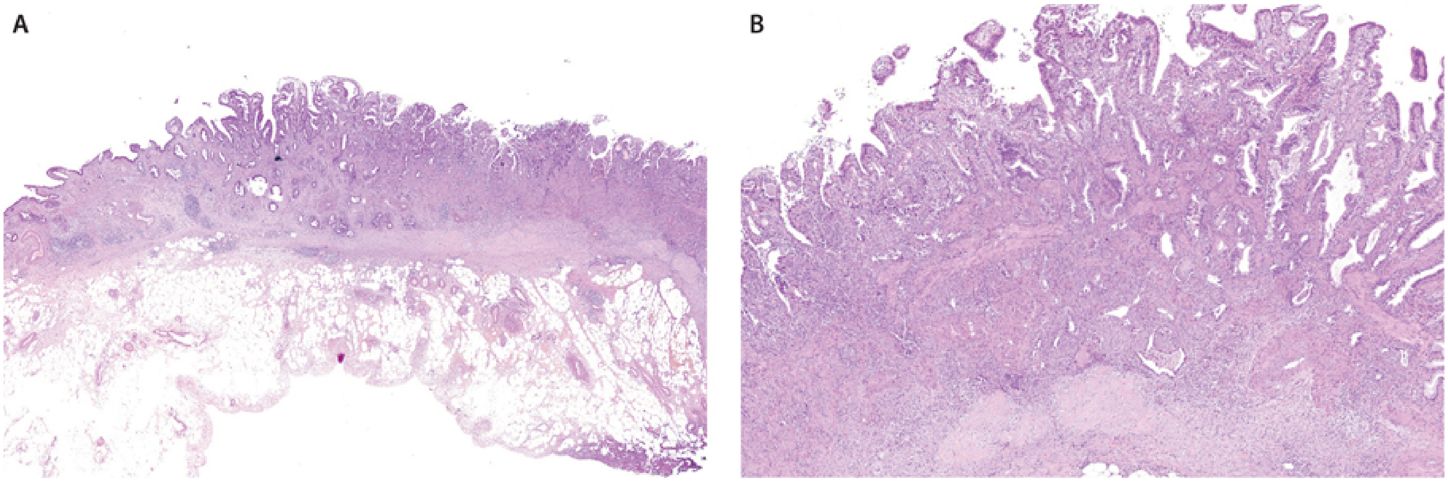

Figure 13-4. Adenocarcinoma. (A) Adenocarcinoma invading the perimuscular connective tissue on the peritoneal side, invading the perimuscular connective tissue. (B) In this field, the adenocarcinoma shows biliary-type histology, but subtyping is not required in the CAP protocol.[8]

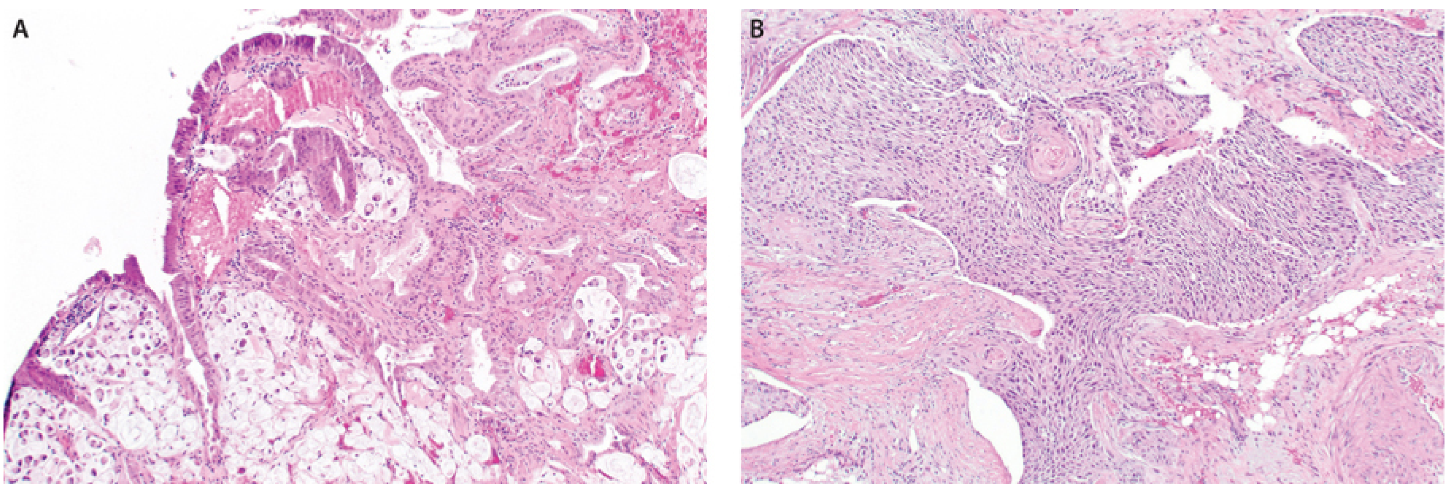

Figure 13-5. Other histologic types. (A) Signet-ring cell carcinoma. (B) Squamous cell carcinoma.

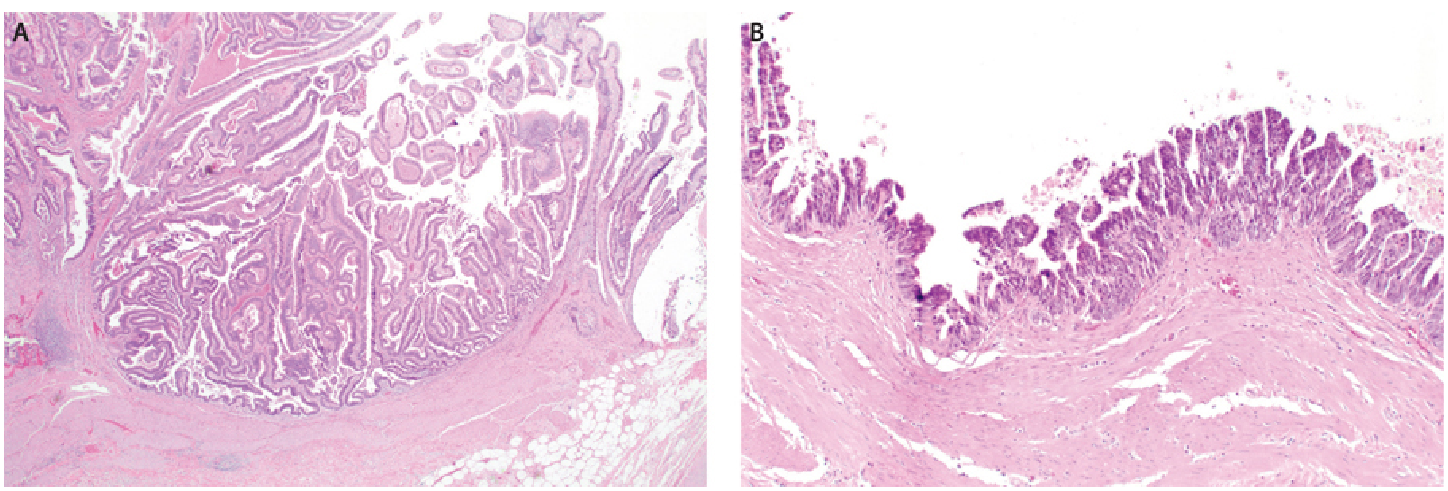

Figure 13-6. Precursor lesions. (A) Intracystic papillary neoplasm (ICPN) with intermediate-grade dysplasia. Focal invasive carcinoma was present in other sections. (B) Biliary intraepithelial neoplasia (BilIN)-3 (high grade).

VII. Common potential pitfalls and solutions

The histologic layers of the gallbladder are more ill defined compared to the gastrointestinal tract. For example, even in an uninjured gallbladder, the muscular layer can be irregular with areas of mucosal invaginations. When the gallbladder is injured, changes to these deep mucosal invaginations (Rokitansky-Aschoff sinuses) may exhibit marked reactive changes as well as dysplasia. When dysplasia involves these deep sinuses, distinguishing it from invasive carcinoma can be difficult.

VIII. What to include in the report?

At minimum, the report should contain the required elements in the CAP cancer protocol. The specimens received and the procedure should be noted. Organs or structures that may be included in a more-complex resection, eg, a radical cholecystectomy, should be mentioned. The tumor site, including the location on the peritoneal side of the gallbladder or the hepatic bed side, is now required in the most recent revision of the CAP cancer protocol (based on the AJCC 8th edition) as this is affects the T stage (pT2a vs pT2b, respectively).[8] The report should also convey critical information that may not be included as well as provide additional clarification to problematic or complex diagnoses. Often, the "top line diagnosis" is used to elaborate on the summarized findings in the synoptic report. In addition, the synoptic report is by definition a summary of the entire case.

An example utilizing both the "top line diagnosis" and the CAP cancer protocol for a simple cholecystectomy follows.

FINAL DIAGNOSIS:

(A) GALLBLADDER, CHOLECYSTECTOMY:

MODERATELY DIFFERENTIATED ADENOSQUAMOUS CARCINOMA (SLIDE MEASUREMENT, 3 CM) INVOLVING THE FUNDUS AND BODY (FREE PERITONEAL AND HEPATIC BED SIDE). (SEE SYNOPTIC REPORT/CAP PROTOCOL.)

BILIARY INTRAEPITHELIAL NEOPLASIA-3 (HIGH GRADE DYSPLASIA) PRESENT AT CYSTIC DUCT MARGIN; all margins are negative for invasive carcinoma.

Background gallbladder with multifocal biliary intraepithelial neoplasia-3 in the body, fundus, neck, and cystic duct.

Synoptic report

Specimen: Gallbladder

Procedure: Simple cholecystectomy (laparoscopic or open)

Tumor Site: Fundus, body

Tumor Size: Greatest dimension – 3 cm

Histologic Type: Adenosquamous carcinoma

Histologic Grade: G2: Moderately differentiated

Microscopic Tumor Extension: Tumor invades perimuscular connective tissue on the peritoneal side without serosal involvement

Margins:

- Cystic duct margin: Uninvolved by invasive carcinoma or high-grade intraepithelial neoplasia
- Liver parenchymal margin: Uninvolved by invasive carcinoma
- Distance of invasive carcinoma from closest margin: 0.2 cm (hepatic bed)
- Lymph-Vascular Invasion: Present
- Perineural invasion: Present
- Regional Lymph Nodes: No nodes submitted or found
- Pathologic Staging (pTNM):
  - TNM Descriptors: Not applicable
  - Primary Tumor (pT): pT2a
  - Regional Lymph Nodes (pN): pNX
  - Distant Metastasis: Not applicable

Additional Pathologic Findings: Dysplasia/adenoma, cholelithiasis, chronic cholecystitis

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14. Gastrointestinal Stromal Tumor (GIST)

Inga-Marie Schaefer, MD; Xiaohua Qian, MD, PhD

The standard treatment of localized gastrointestinal stromal tumor (GIST) is surgical resection. Since GISTs are usually well-circumscribed tumors, wide excisions are usually not necessary, and relatively narrow margins (~1.0 cm) are generally adequate. Since GISTs rarely metastasize to lymph nodes, lymphadenectomy is generally unnecessary, except for cases presenting with enlarged or grossly suspicious lymph nodes. GISTs generally metastasize to the peritoneum or liver and extremely rarely to the lungs or bone. The prognosis of GIST patients is variable and depends on genotype, location, size, and mitotic activity.[1,2] While many GISTs are initially diagnosed on needle biopsy samples,[3,4] risk assessment, based on the criteria adopted in a National Comprehensive Cancer Network (NCCN) Task Force report on GIST, is generally deferred to the pathologic examination of the resected tumor.[1,5] Both tumor size and mitotic rate, which can only be precisely evaluated on resected tumors, are essential parameters in the current risk stratification scheme. The 8th edition of the TNM classification incorporates parameters of the NCCN risk stratification system (Table 14-1).[6,7]

Table 14-1. Risk Stratification of Primary GIST (National Comprehensive Cancer Network [NCCN] Guidelines 2007)[16]

Tumor Parameters		Risk of Progressive Disease* (%)			
Mitotic index	Size (cm)	Gastric	Duodenum	Jejunum/ileum	Rectum
≤5 per 5 mm²	≤2	None (0%)	None (0%)	None (0%)	None (0%)
≤5 per 5 mm²	>2 ≤5	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
≤5 per 5 mm²	>5 ≤10	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
≤5 per 5 mm²	>10	Moderate (10%)	High (52%)	High (34%)	High (57%)
>5 per 5 mm²	≤2	None†	High†	Insufficient data	High (54%)
>5 per 5 mm²	>2 ≤5	Moderate (16%)	High (73%)	High (50%)	High (52%)
>5 per 5 mm²	>5 ≤10	High (55%)	High (85%)	Insufficient data	Insufficient data
>5 per 5 mm²	>10	High (86%)	High (90%)	High (86%)	High (71%)

* Defined as metastasis or tumor-related death.
† Small numbers of cases.

GISTs comprise a molecular and morphologic spectrum: most GISTs harbor activating mutations in the *KIT* (~75%, exons 8, 9, 11, 13, 14, and 17) or platelet-derived growth factor receptor A (*PDGFRA*) (~10%, exons 12, 14, and 18) receptor tyrosine kinase genes (Figure 14-1).[2] Less frequent subtypes of GIST exhibit genomic or epigenetic inactivation of the succinate dehydrogenase complex (*SDH*) complex leading to SDH deficiency, which can be observed in ~10% of GISTs, and another 1% to 2% of GISTs harbor inactivating *NF1* mutations (Figure 14-2).[2] SDH-deficient GIST is also associated with cancer genetic syndromes, such as nonhereditary Carney triad and the autosomal-dominant Carney-Stratakis syndrome.[8] In addition, the current standard NCCN risk stratification criteria for assessing the malignant potential of GISTs does not predict the clinical behavior of this group of tumors.[9]

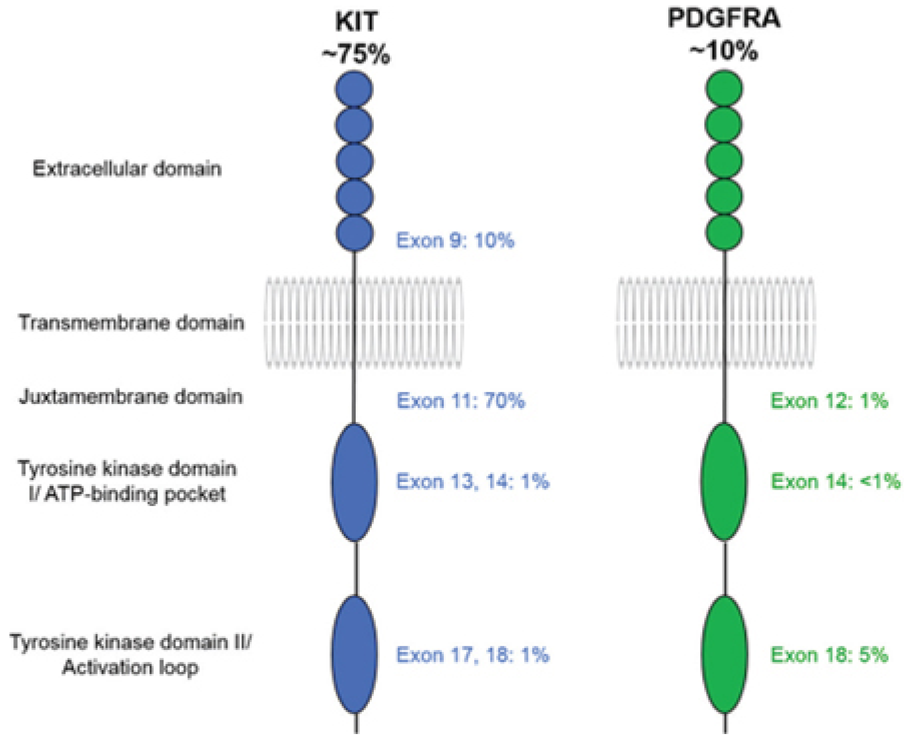

Figure 14-1. Receptor tyrosine kinase mutations in GIST (adapted from Schaefer et al[2]).

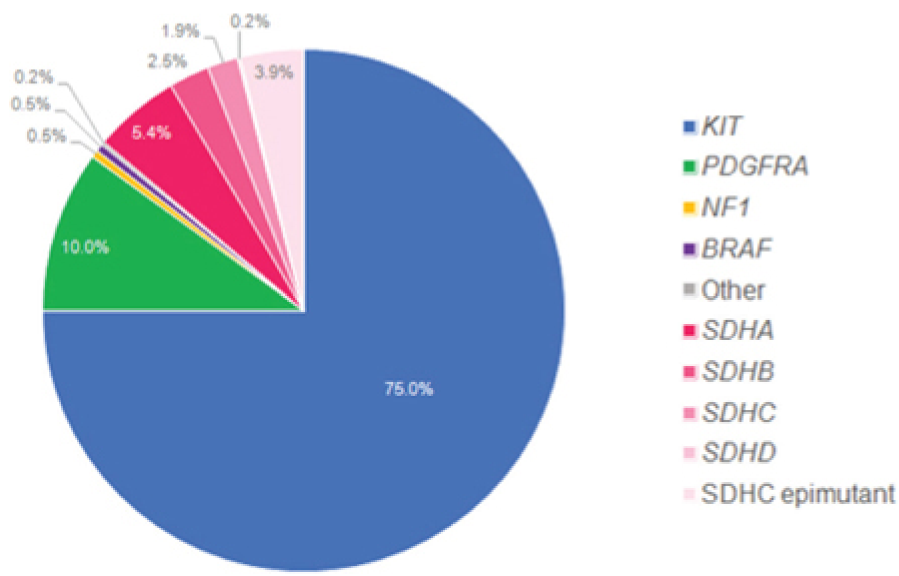

Figure 14-2. Frequency of molecular subtypes of GIST (adapted from Schaefer et al[2]).

GISTs may arise anywhere along the entire length of the gastrointestinal tract, with stomach being the most common site (60%), followed by small intestine (30%) and less often colon and esophagus. Some primary tumors are found to arise in mesenteric fat or omentum without an obvious attachment to bowel wall. Extremely rare cases of GIST occur outside the gastrointestinal tract, specifically in lungs and in the female genital tract.[10]

This chapter provides an overview of the appropriate gross and histologic evaluation of GIST resection specimens, with a focus on gastrointestinal tract tumors, judicious use of immunohistochemistry and molecular studies, and the pertinent information to be included in the pathology report. Depending on tumor location and size, surgical resection can be achieved either endoscopically or through an open approach and be either more localized (eg, partial gastrectomy for small gastric GISTs) or extensive (eg, pancreaticoduodenectomy for duodenal GISTs).

I. Indications for GIST resection

1. The standard treatment for localized GIST is surgical excision.

2. In the metastatic setting, debulking or "cytoreductive" surgery is sometimes performed to remove all grossly identifiable tumor after neoadjuvant treatment with tyrosine kinase inhibitors (TKIs) and to improve clinical outcomes.

II. What do we expect to see in the GIST specimen

GISTs are grossly and histologically well-circumscribed tumors, and therefore excision of wide margins is not necessary. Depending on tumor size and anatomic location, a partial gastrectomy or segmental resection of the small or large intestine is usually sufficient to achieve clear margins. Description of the resection specimen includes the pertinent findings in the tumor of interest and any information important for risk stratification (tumor location and size) and staging (such as distance to margins and appearance of the serosal surface), as well as the presence or absence of adjacent normal tissues and any other involved organs. Communication with the operating surgeon for specimen orientation is important in cases with complicated anatomic relations, grossly close margins, or disrupted specimens.

III. Typical macroscopic appearance of GIST specimens

Grossly, GISTs are well-circumscribed tumors arising in the gastric or intestinal wall (Figure 14-3A,B). They show a tan to whitish and sometimes whorled cut surface; areas of myxoid change and hemorrhage or central infarction, commonly present in larger tumors. While true coagulation necrosis is a rare finding in GIST and mostly occurs in rapidly growing, aggressive tumors, hyalinization and fibrosis can be observed as treatment effect after neoadjuvant TKI therapy.

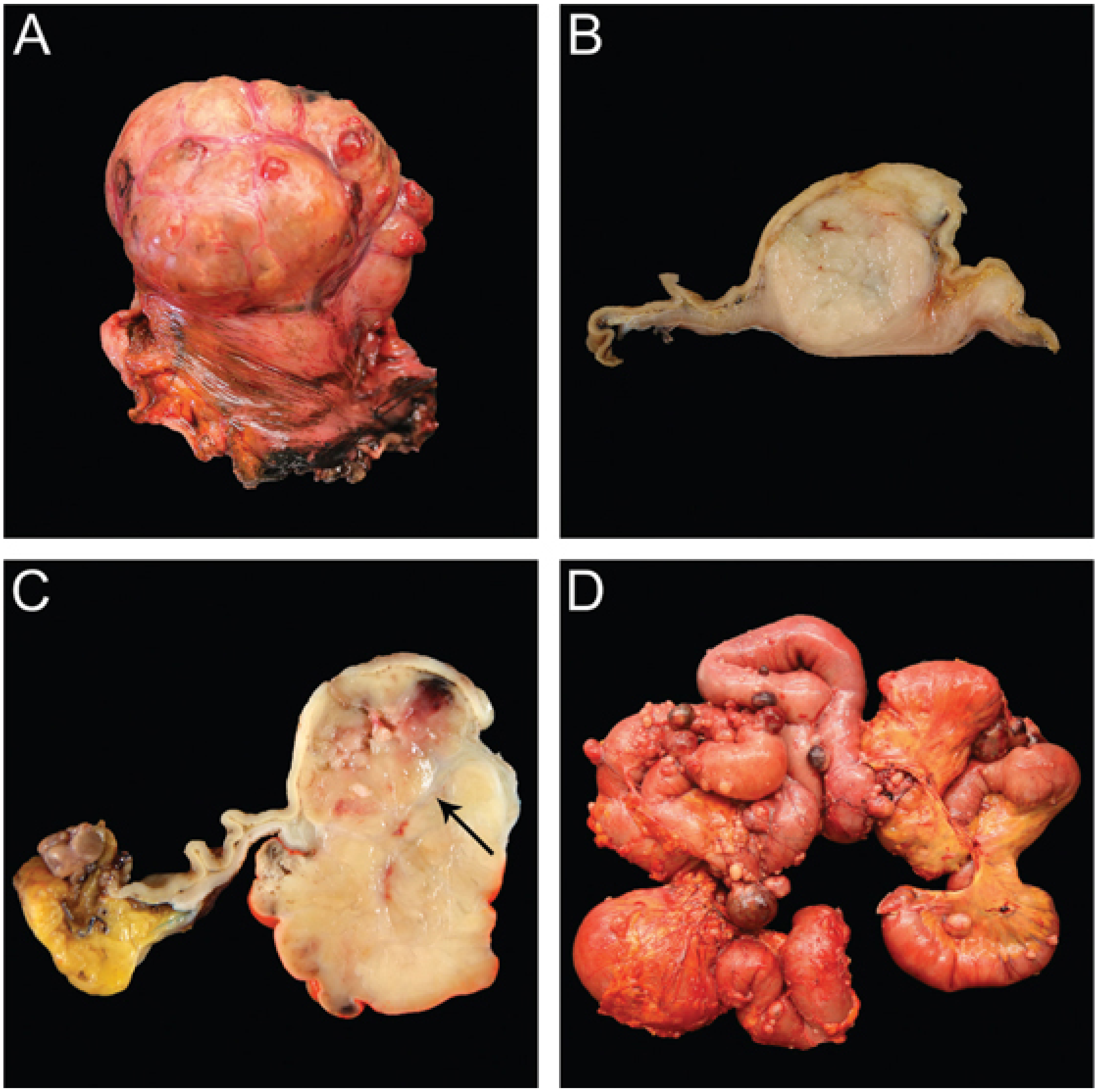

Figure 14-3. Gross photographs. GISTs are well-circumscribed tumors that present as a subserosal or submucosal mass (A, fresh tissue). Close surgical resection is often adequate to achieve tumor-free margins. GISTs display a solid, tan to whitish, occasionally whorled cut surface and well-defined tumor margins (B, after fixation). SDH-deficient GISTs (C, after fixation) show a characteristic multilobulated appearance with nodules separated by thick fibrous bands (arrow). Metastatic GIST presenting as multiple serosal and mesenteric nodules (D, fresh tissue).

Except for SDH-deficient GISTs, lymph node metastasis is extremely rare, and therefore oncologic lymphadenectomy is generally not performed by the surgeon.

KIT-mutant GISTs, the most common subgroup, may occur anywhere throughout the tubular gut. *PDGFRA*-mutant GISTs have a predilection for gastric location. SDH-deficient GISTs virtually only occur in the stomach, whereas GISTs that arise in association with neurofibromatosis type 1 (NF1) are generally limited to the small intestine.

Rare syndromic cases, ie, SDH-deficient GISTs associated with Carney-Stratakis syndrome or Carney triad, NF1-associated GISTs, and GISTs in patients with germ-line *KIT* mutation, often present at a younger age and are more often multifocal than sporadic GISTs. SDH-deficient GISTs show a characteristic plexiform or multilobulated appearance, which is pathognomonic for this subtype of GIST (Figure 14-3C).

IV. Dissection technique of GIST specimens

1. Review relevant clinical and imaging information.

- As for any oncologic surgical resection specimen, awareness of pertinent preoperative features, such as patient age, sex, tumor-related symptoms, cancer history, neoadjuvant tyrosine kinase treatment, anatomic

location, number and size of tumors, and relationship of tumor to organs and serosal surface will help avoid potential discrepancies.

2. Orient the specimen.

- Orientation of GIST specimens is usually straightforward as the tumors are usually well circumscribed (Figure 14-3).

3. Record the specimen weight and dimensions.

4. Use indelible ink of different colors to mark the specimen margins (proximal, distal, medial, lateral, and mesenteric if present).

5. Serially section the tumor.

6. Describe the tumor, including its:

- Size in three dimensions, to the nearest millimeter
- Location and relationship to margins and to other structures (if present)
- Circumscription, encapsulation, lobulation, uniformity, color, consistency, hyalinization, cystic change, hemorrhage, necrosis (rare in GIST), and assess percentage of viable and nonviable appearing tumor (if the tumor was treated with neoadjuvant tyrosine kinase inhibitors)
- Relation to serosal surface and describe any serosal rupture

7. Submit fresh tumor tissue for evaluation by molecular studies.

8. Bank fresh tissue for research (if applicable), following the institutional guidelines, if a research protocol is available.

9. Allow the specimen to fix overnight, most commonly in 10% neutral-buffered formalin.

10. Submit representative sections of tumor for light microscopy, including its relationship to margins and to other structures (if present); one should submit at least one section per centimeter of tumor and, if applicable, include viable and nonviable areas; small tumors can be submitted in their entirety.

11. Serially section the remainder of the specimen and examine for the presence of additional lesions.

12. Submit representative sections of nontumoral organ/tubular gut.

13. Submit any grossly suspicious/enlarged lymph nodes.

V. Gross description of GIST specimens, using paragraph system

As described in other chapters, Raymond's paragraph system will be used to describe the GIST specimen.

Example of gross description of a GIST specimen

Received fresh, labeled "partial gastrectomy," is a portion of stomach (8.6 x 7.0 x 1.6 cm), with a short suture indicating proximal, and a long suture designating distal per surgeon. The proximal stapled resection margin measures 8.5 cm in length and is inked blue, and the distal stapled resection margin measures 6.8 cm in length and is inked black. There is a well-circumscribed solid mass with a tan cut surface (4.8 x 4.0 x 3.8 cm) that is 1.4 cm from the proximal stapled resection margin and 1.1 cm from the distal stapled resection margin. The mass is covered by intact serosa (inked orange) and appears grossly confined to the gastric wall. The mucosal surface is smooth, without ulceration and focal lesions. No lymph nodes are identified grossly. Representative sections of the mass are submitted for cytogenetic/molecular studies, tissue bank, and research. Gross photographs are taken. Representative sections are submitted for histologic evaluation.

A1: Proximal gastric resection margin, perpendicular

A2: Proximal gastric resection margin, perpendicular

A3-A7: Representative sections of the mass, including relation to serosal surface

A8: Uninvolved stomach

VI. Common pathologic findings in GIST specimens

Histologically, GISTs are well-circumscribed tumors (Figure 14-4A) and show either spindled (~70%) (Figure 14-4B), mixed (~10%) (Figure 14-4C), or epithelioid (~20%) (Figure 14-4D) cytomorphology. *PDGFRA*-mutant GISTs have a predilection for epithelioid cytomorphology, sometimes with prominent cytoplasmic vacuoles. NF1-associated GISTs generally show spindled or mixed cytomorphology, whereas

SDH-deficient GISTs virtually always exhibit epithelioid or mixed cytomorphology and a multinodular appearance.

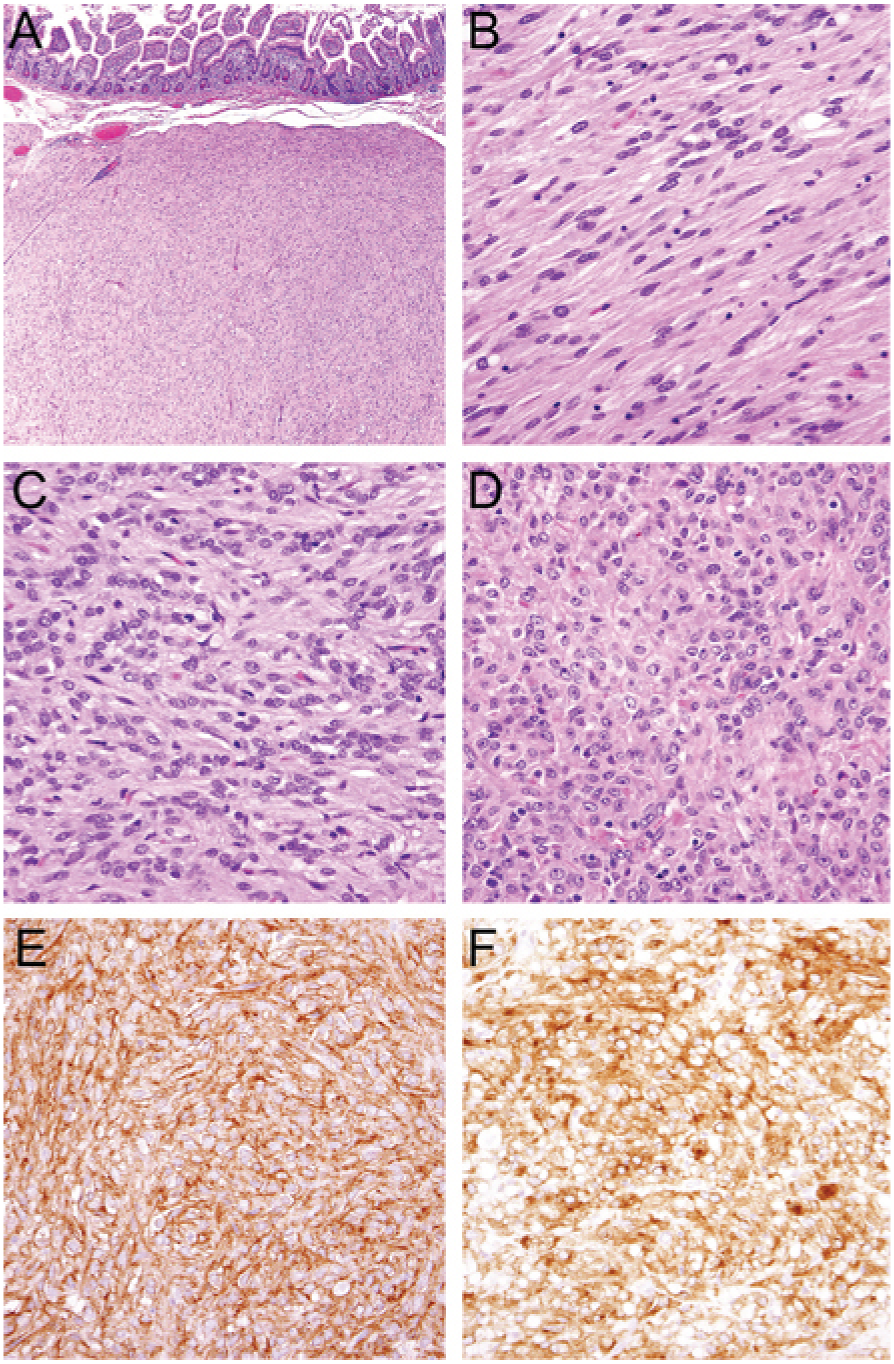

Figure 14-4. Photomicrographs: *KIT*-mutant GIST. GISTs usually present as a sharply demarcated submucosal (A) mass and can show spindled (B), mixed (C), or epithelioid morphology (D). The majority of GISTs are positive for DOG1 (E) and KIT (F).

Immunohistochemical staining for DOG1 (Figure 14-4E) and KIT (Figure 14-4F) is positive in 98% and 95% of cases, respectively.[11,12] Approximately 70% of cases express CD34, and PDGFRA immunohistochemistry is usually positive in *PDGFRA*-mutant GISTs.[13] Less than 40% of GISTs are positive for smooth muscle actin, 5% for S100 protein (usually focal), 5% for desmin (usually focal), 1% to 2% are positive for keratin (weak/focal), and rarely expresses Melan-A.

While all *KIT/PDGFRA/NF1*-mutant GISTS show retained expression of SDHB and SDHA by immunohistochemistry, the SDH-deficient GISTs are characterized by loss of SDHB expression (Figure 14-5):

inactivating mutations in *SDH* subunits A, B, C, or D or *SDHC* promoter methylation led to loss of function of the SDH complex, which results in loss of SDHB protein expression (Figure 14-5A-C). SDHB negativity is therefore not specific for a certain type of *SDH* (epi-)mutation. In contrast, loss of SDHA expression is only observed in GISTs with underlying *SDHA* mutation (Figure 14-5D-F).

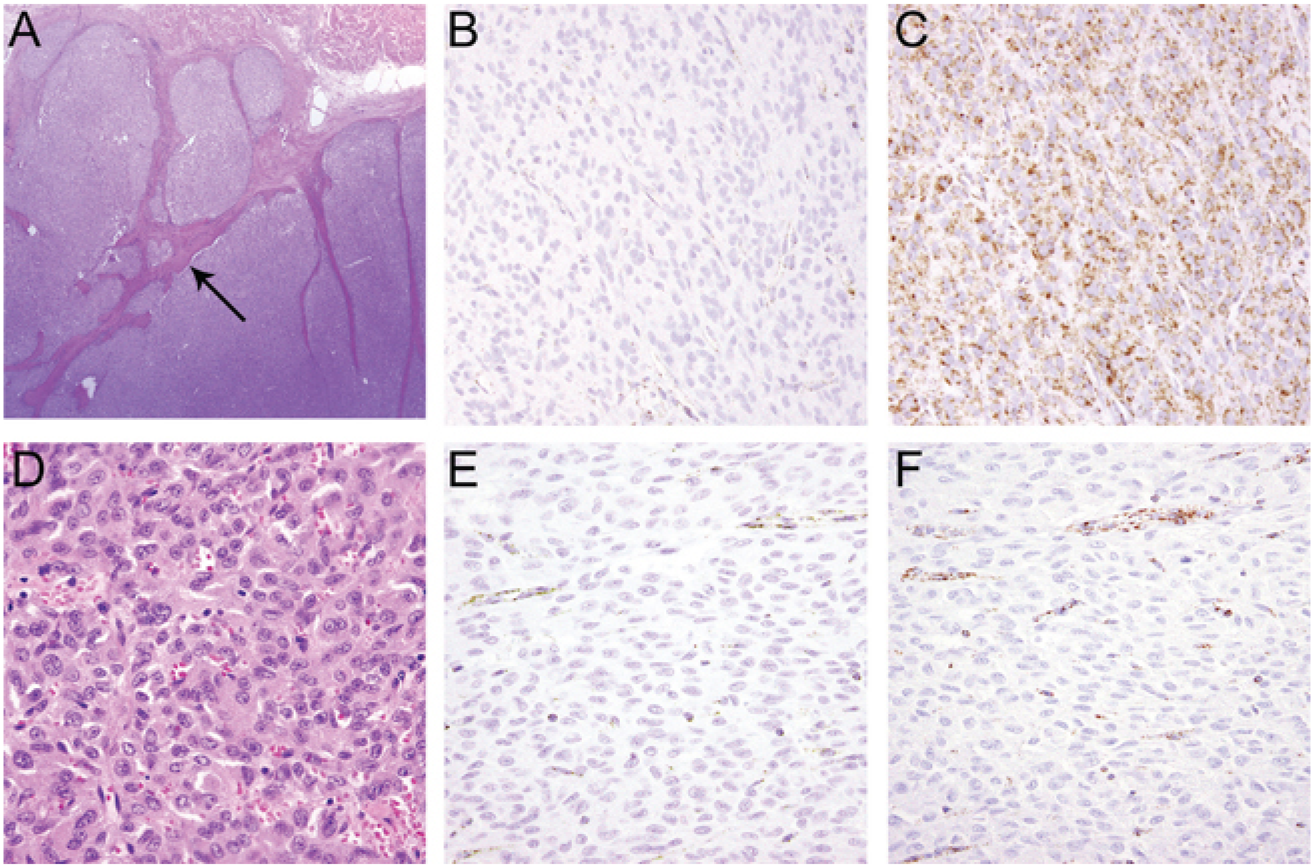

Figure 14-5. Photomicrographs: SDH-deficient GIST. The SDH-deficient GISTs demonstrate a characteristic plexiform or multilobulated appearance at low magnification (A, H&E stain) and usually an epithelioid cytomorphology at high magnification (D, H&E stain; arrow: thick fibrous bands between the nodules). All SDH-deficient GISTs have in common a loss of SDHB expression (B and E). SDH-deficient GISTs without *SDHA* mutation show loss of SDHB expression (B) and retained staining for SDHA (C). *SDHA*-mutant GISTs with an epithelioid morphology (D, H&E stain) show loss of SDHB expression (E) but, in addition, also negativity for SDHA (F). Vessel walls serve as a positive internal control.

Sequencing of the *KIT* and *PDGFRA* genes is not required to establish a diagnosis of GIST but provides valuable information that is useful to guide treatment decisions since TKI response and resistance is often determined by the underlying primary *KIT/PDGFRA* mutation.

VII. Common potential staging pitfalls and solutions

Accurate assessment of mitotic activity is essential for risk stratification of a given GIST as it determines the patient's prognosis and affects decisions about adjuvant TKI therapy. It is important to note that mitoses are counted in a 5 mm^2 area, which—depending on the type of microscope used—equals 20 to 25 high-power fields in most modern microscopes with wider 40x lenses/fields (and no longer 50 high-power fields, as previously reported for older models). In addition, caution should be made to avoid over counting by mistaking apoptotic figures or mast cells as mitoses and undercounting by missing the mitotic hot spots. In addition to mitotic count, accurate measurement of tumor size in the fresh, unfixed state is important to avoid shrinking artifact, which may affect risk assessment.

Tumor rupture is extremely rare but may occur in very large, friable GISTs. Since tumor rupture represents an adverse prognostic factor, documentation of an intact versus ruptured peritoneal surface should be included in the gross description. Some fragmented tumor specimens obtained via laparoscopic resection may not

represent a truly ruptured tumor and may not pose a risk for peritoneal spread. Therefore, in cases where the serosal surface appears grossly disrupted, communication with the surgeon and/or review of the intraoperative report may be helpful to ensure that the tumor rapture status is correctly documented.

Since risk assessment is used to predict the rate of malignant behavior, it becomes irrelevant in cases that present with either prior or concurrent metastases.

VIII. What to include in the pathology report

The final pathology report of a primary GIST resection specimen should include the pertinent parameters for risk stratification, staging, as well as assessment of treatment response in patients who received neoadjuvant TKI therapy. Only the definitive primary tumor resection specimen is required to have core elements reported in a College of American Pathologists (CAP) synoptic format. Recurrent or metastatic tumor resected at a different time than the primary tumor is not required to use the CAP synoptic format.

Information provided in the synoptic report should include the procedure performed, the tumor site, tumor size, tumor focality, histologic type, mitotic rate, presence or absence of necrosis, histologic grade, risk assessment (NCCN guideline, see Table 14-1), the status of resection margins, status of regional lymph nodes, and pathologic stage classification (pTNM, American Joint Committee on Cancer [AJCC] 8th edition); optional reportable data elements include additional pathologic findings, the results of ancillary studies (immunohistochemistry studies and/or molecular genetic studies), the type of preresection treatment and the treatment effect, and finally case comments.

Since a small subset of GISTs is syndromic and can be associated with *KIT* germ-line mutations, Carney-Stratakis syndrome, Carney triad, or NF1. Close communication between the clinical team and pathologist is essential to recognize features that would uncover a syndromic association, which include young age, personal/family history of GISTs, or manifestations associated with Carney-Stratakis syndrome (paraganglioma, pulmonary chondroma) or NF1. In such cases, a comment to suggest a syndromic association should be included in the end.

An example of a surgical pathology report is provided below.

FINAL DIAGNOSIS

Stomach, partial gastrectomy:

Gastrointestinal stromal tumor (4.8 cm), mixed spindle cell and epithelioid type, low risk category, pT2N0 (see synoptic report).

Synoptic report

Procedure: Partial gastrectomy

Tumor size: 4.8 cm

Tumor focality: Unifocal

Histologic type: Gastrointestinal stromal tumor, mixed spindle cell and epithelioid type

Mitotic rate: 2/5 mm^2

Necrosis: Not identified

Preresection treatment: No known preresection therapy

Treatment effect: No known presurgical therapy

Histologic grade: G1: Low grade; mitotic rate ≤5/5 mm^2

Risk assessment: Low risk

Margins: Uninvolved by GIST

Regional lymph nodes: No lymph nodes submitted or found

Pathologic stage classification (AJCC 8th edition): pT2N0

Ancillary studies: Immunohistochemistry demonstrates the following staining profile in lesional cells:

Positive - KIT, DOG1 SDHB (intact of expression)

Negative - S-100 protein.

The above information is a modification of the AJCC cancer staging protocol and CAP cancer staging protocol for GIST.

In SDH-deficient GIST resection cases, the following comment is suggested to be included in the end of the report.

Comment: This epithelioid GIST displays a multinodular/plexiform growth pattern (is associated with lymph node metastases) and shows loss of expression of the mitochondrial protein succinate dehydrogenase subunit B (SDHB) by immunohistochemistry. These findings are characteristic of a distinctive class of gastric GISTs ("succinate dehydrogenase-deficient GISTs") that arise in children, in patients with Carney triad and Carney-Stratakis syndrome, and occasionally in adult patients (5-10% of gastric GISTs overall). Unlike conventional adult GISTs, these tumors lack mutations in *KIT* and *PDGFRA*; a subset of such tumors arises in patients with germline mutations in one of the succinate dehydrogenase subunit genes. Risk stratification criteria for conventional adult GISTs do not reliably predict behavior for this group of tumors, although they have a significant potential for metastasis to lymph nodes, the liver, and peritoneum. Metastatic lesions typically show relatively indolent progression and limited (if any) response to imatinib mesylate.

Of note, loss of SDHA protein expression specifically predicts *SDHA* mutations (if loss of SDHA expression is detected).[14,15]

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15. Liver

Khela R. Pursell, PA(ASCP); Murli Krishna, MD

Introduction

Liver resections may be partial or complete and are performed for both neoplastic and nonneoplastic conditions. The extent and type of a partial resection often depend on the location of the mass in the context of the functional anatomy, the need to preserve uninvolved liver parenchyma, and the presence or absence of background liver disease. Partial resections may be anatomic (based on the segmental anatomy) or nonanatomic. In patients with significant background liver disease, partial resections may not be feasible. In selected patients, this clinical setting may lead to an evaluation for liver transplantation.

Thorough gross evaluation and sampling of the resected liver is critical for obtaining accurate information regarding the lesions and/or disease process. For malignant lesions, it has a significant impact on the final reported histologic and staging information used for patient management. Initial sectioning may render the specimen disrupted and therefore is often the best opportunity for obtaining accurate information. It is important for the initial handling to be carefully considered in the context of available clinical information, including findings on imaging, prior pathologic evaluation (eg, cytology), prior treatment (eg, tumor embolization), and the need for obtaining tissue for ancillary studies or research. In some cases, communication with the surgeon may be important before proceeding with specimen handling.

I. Indications for liver resections

Partial hepatectomy

In over two thirds of cases, the indication for a partial resection is malignancy, with metastatic colorectal carcinoma being the most common, followed by hepatocellular carcinoma (HCC). Among the benign indications for partial resections, liver cell adenoma is the most common neoplasm; however, nonneoplastic conditions comprise about two thirds of the cases (eg, cystic disease, focal nodular hyperplasia).[1]

The terminology used to designate liver resections is based on the segmental anatomy. Right hepatectomy (hemihepatectomy) involves resection of segments V-VIII, and right lobectomy (extended right hepatectomy or right trisegmentectomy) involves resection of all segments lateral to the umbilical fissure (segments IV-VIII, and may include segment I). The umbilical fissure corresponds to the attachment of the falciform ligament and ligamentum teres. Left hepatectomy involves resection of segments II-IV. Extended left hepatectomy (left trisegmentectomy) includes resection of segments II-IV, as well as segments V and VIII of the right lobe. Left lobectomy includes the two segments medial to the umbilical fissure (II and III)[2] (Figure 15-1).

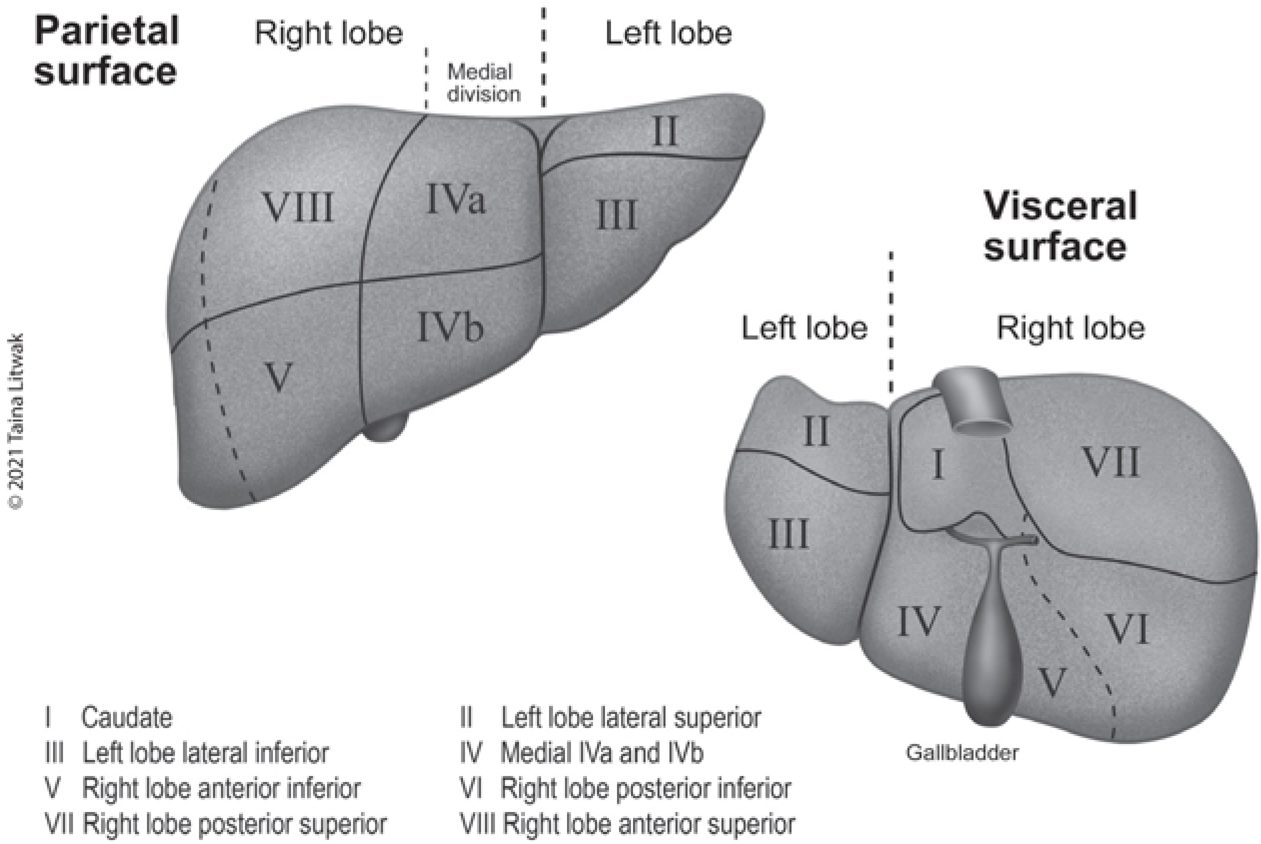


Figure 15-1. Segmental anatomy of the liver.

Total hepatectomy (explants)

Orthotopic liver transplantation involves removal of the entire liver and replacement with a donor organ. Transplantation is performed for a variety of indications, including acute liver failure, complications of cirrhosis, and systemic complications of metabolic or chronic liver disease.[3] Approximately 10% to 20% of liver explants contain malignancies, most commonly hepatocellular carcinoma. Most of these tumors are previously diagnosed; however, previously undiagnosed hepatocellular carcinoma may be discovered as single or multiple nodules, including diffusely infiltrative tumors. Other rare tumors for which transplantation may be performed include epithelioid hemangioendothelioma and metastatic low-grade neuroendocrine tumors.

II. Radiation safety protocol

Special consideration should be given to handling of liver specimens containing tumors treated with transarterial radio-embolization. The treatment involves injection of radioactive microspheres targeted at the tumor. The microsphere preparations in current use are TheraSphere and Sir-Spheres, both containing Y-90. Dissection of radioactive specimens without appropriate precautions may lead to contamination of the work environment and individuals. Handling of such specimens should be done within a radiation safety protocol, which includes reliable communication with the surgical team, clear specimen labeling, scanning of the specimen for radioactivity, dissection of specimen within a dissecting tray, isolation and monitoring of the subsequent processing, and proper disposal of radioactive material (Figure 15-2).

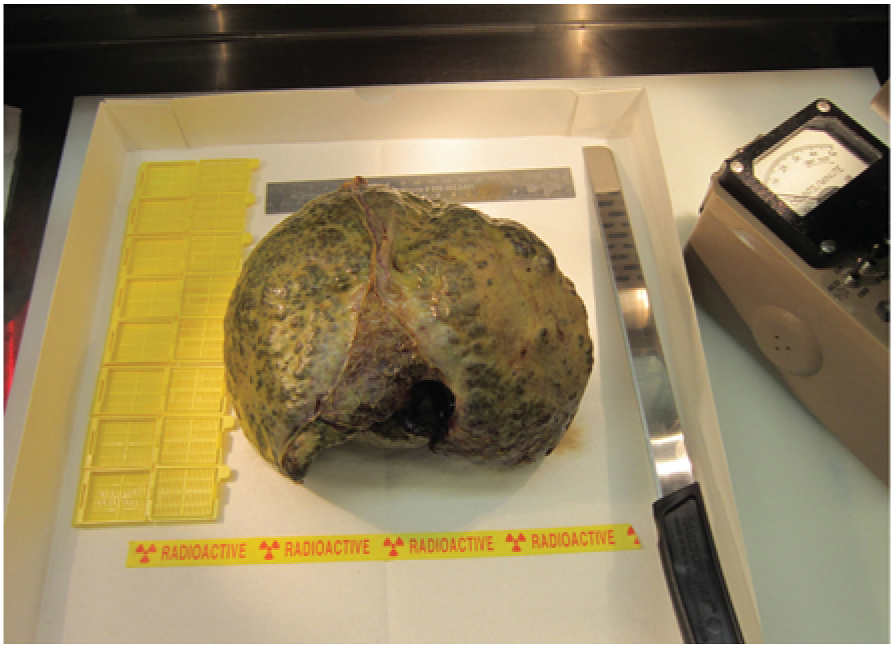


Figure 15-2. Radiation safety protocol should include handling the specimen in an isolating tray confining the specimen and materials used. A detector should be used to assess for radioactivity.

III. What do we expect to see in hepatectomy specimens macroscopically

In a partial hepatectomy specimen, there is both a capsular surface and a surgical surface, the latter representing the surgical margin. The capsular surface may be smooth or irregular, bulging or depressed depending on the underlying lesion. The surgical surface is irregular or may be disrupted. Sectioning of the specimen should include the lesion and its relationship to the parenchymal margin and other structures as applicable, such as the vein and bile duct. There may also be a need to evaluate biliary or vascular margins if necessary.

The lesion may be a well-defined mass (eg, HCC, metastatic carcinoma), diffusely infiltrative (epithelioid hemangioendothelioma), a variably dilated duct, or a cyst (eg, intraductal papillary neoplasm, hepatobiliary cystadenoma) (Figures 15-3 and 15-4).

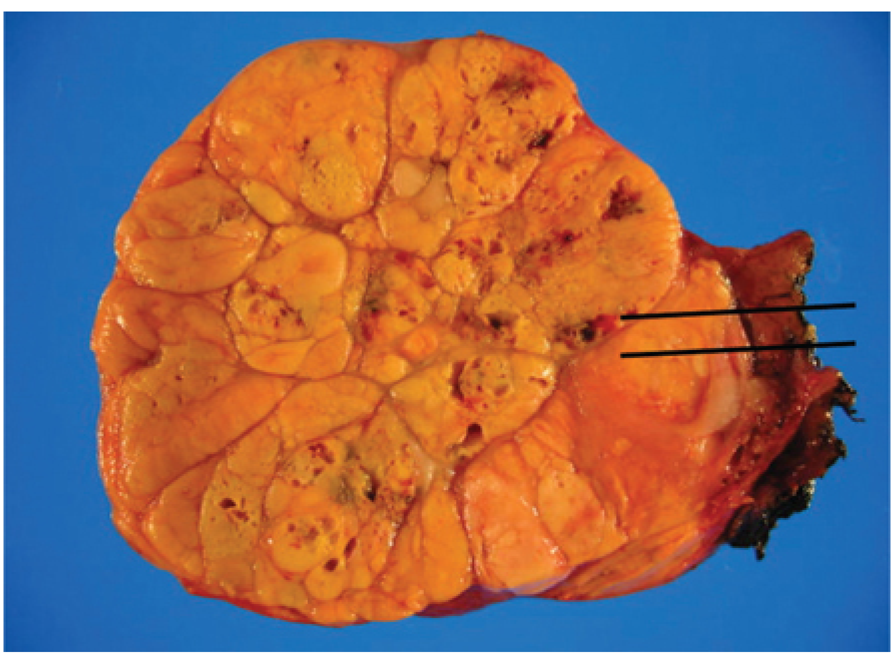


Figure 15-3. Partial resection of liver with hepatocellular carcinoma. The lines indicate recommended method of sectioning to optimally evaluate the margin.

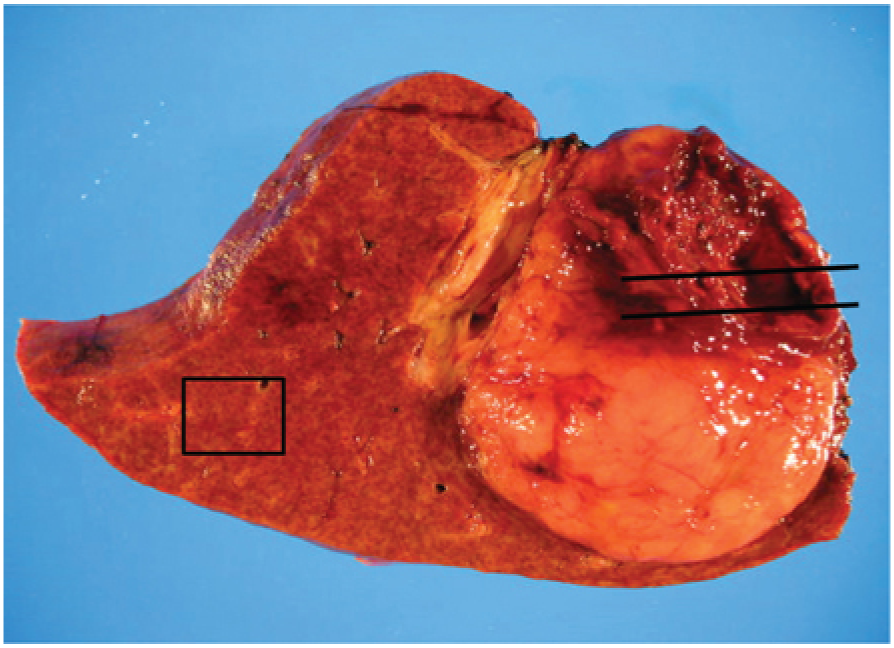


Figure 15-4. Partial resection of the liver with metastatic gastrointestinal stromal tumor. Note the proximity to the surgical margin, which is best assessed with perpendicular sections (lines). Tissue representing the background liver may be submitted from an area away from the mass (rectangle).

In a total hepatectomy specimen (explant), the surface of the liver is commonly nodular because of cirrhosis. Similar to partial hepatectomies, a mass or lesion may be evident underneath the surface. Particular attention must be directed at the hilar structures, with appropriate evaluation for mass lesions (eg, hilar cholangiocarcinoma) and for patency of the bile ducts and portal vein. Biliary strictures may indicate malignancy or involvement by primary sclerosing cholangitis. The portal vein may contain a thrombus or even intravascular growth of tumor that was previously not detected (eg, hepatocellular carcinoma). Appropriate sections must be obtained to represent the biliary and vascular margins, as well as any gross abnormalities. The hepatic veins must be examined for patency; the vein margin must be submitted for histology if applicable, such as in cases with epithelioid hemangioendothelioma. Hilar lymph nodes must be documented and submitted for histology. If the gallbladder is present, gross examination and sectioning should be performed as recommended for the gallbladder. Cut sections of the liver will commonly show cirrhosis; however, cases transplanted for noncirrhotic portal hypertension or acute liver failure will not show a cirrhotic morphology. Size, location, and number of lesions should be documented and sectioned for histology. Necrosis of the tumor and surrounding liver is commonly seen in cases with prior embolization treatment. In a minority of cases, lesions are present that were not detected with pretransplant imaging studies. Most commonly the tumors are either small or diffuse hepatocellular carcinomas, which could not be resolved with imaging. Thus, careful examination of the cut surfaces is necessary for nodules with unusual appearance (Figure 15-5).

Figure 15-5. Liver explant with cirrhosis. Serially sectioning the liver (0.5-1.0-cm intervals) is helpful in identifying small lesions, including those not seen in pretransplant imaging studies.

IV. Typical gross photos of liver specimens

Gross photographs may be obtained for documentation, teaching, presentation or publication. A ruler and specimen identification number are helpful for reference. Photographs may include the external surface and cut surface(s), and should include lesions (Figures 15-3 through 15-5).

IV. Dissection technique: step by step description

1. Weight and measurements

All specimens should be weighed and measured in three dimensions prior to sectioning. Any surface abnormalities should be noted and measured as applicable.

2. Fixation

For optimal histology, the liver tissue must be adequately fixed. For specimens that are examined and sectioned fresh, several hours of formalin fixation may be adequate. Partial hepatectomies that are received in formalin also need several hours of fixation. Explants should be fixed for at least 24 hours, allowing formalin to penetrate deep into the tissues. Formalin exposure can be increased by initially sectioning the specimen and allowing it to fix overnight before further detailed examination. During this step, orientation of the tissue should be maintained. For grossly cirrhotic livers that do not appear to have adequate formalin penetration, random sections for histology may be obtained from peripheral locations.

3. Orientation of the specimens

For partial hepatectomy specimens, orientation may not be possible or necessary unless it is provided by the surgeon. If the surgeon plans to re-excise a specific area of the margin involved by the tumor, orientation is necessary for providing meaningful intraoperative consultation. In such situations, if possible, it is often helpful to review the specimen with the surgeon.

For total hepatectomy specimens, orientation is usually not difficult. Before sectioning, important landmarks must be noted; these include the umbilical fissure, the gallbladder, and the inferior vena cava fossa. These help in orienting the specimen with reference to its surgical/functional anatomy. Awareness of the hilar anatomy helps in location and dissection of the hilar structures; the bile duct and the hepatic artery usually lie anterior to the portal vein.

4. Documentation of resection margins

For partial hepatectomy specimens, the parenchymal margin should be inked; care should be taken so that the ink does not seep into the deeper tissues, as the surgical margin may be irregular and disrupted. The margin

is best evaluated after serially sectioning the specimen at 0.5-cm intervals perpendicular to the margin. The area of grossly closest margin is submitted for histology. If necessary, biliary or vascular margins may also be submitted for histology.

For total hepatectomy specimens, the margins generally include the hilar biliary and vascular margins. As mentioned above, evaluation of the hepatic vein margin may be necessary in tumors with a propensity for intravascular growth, such as with epithelioid hemangioendothelioma.

5. Sectioning and submitting tissue for histology[4-6]

Partial hepatectomy specimens should be sectioned at approximately 0.5-cm intervals perpendicular to the parenchymal margin. The orientation of the specimen is maintained while examining the cut surfaces for lesion(s).

For total hepatectomy, the specimen is similarly sectioned at intervals of approximately 0.5 cm, beginning from the left or right lobe, while the overall orientation, relationships to major landmarks (eg, the hilum and anatomical planes), and segmental anatomy is maintained. Locations of parenchymal lesions are described with respect to the segmental anatomy. Occasionally the liver may contain a transjugular intrahepatic portosystemic shunt (TIPS); the patency of the shunt should be documented. It is often helpful to correlate the findings with imaging studies; however, small or diffuse abnormalities may not be detected on imaging. Small nodules with an appearance that does not resemble background cirrhotic nodules should be sampled, as these may resemble small hepatocellular carcinomas. Variations within the lesions should be sectioned for histology, as these may represent histologic variations (eg, tumor grade and mixed tumors).

The number of sections for histology should be guided by the tumor size and gross variations. Tumors treated prior to surgery (systemic or embolization) may be variably necrotic or fibrotic and may require extensive sampling. Cystic lesions should be carefully examined for mural nodules, and these areas should be extensively sampled to evaluate for malignancy.

6. Tissue banking

Tissue may be triaged for research or tissue banking as per institutionally approved protocols and established guidelines. The collection and protocol number should be recorded in the report. Priority should always be given to using tissue for diagnosis and ancillary studies relevant to patient care. If necessary, tissue stored for research may be obtained and used for clinical care.

V. Examples of gross descriptions using the paragraph system

Partial hepatectomy

The specimen is received fresh and consists of a portion liver labeled “segment V mass.” No specimen orientation is provided by the surgeon.

The specimen measures 6.0 x 3.5 x 3.0 cm. The capsular surface is smooth, and includes the lower border of the liver. The surgical margin is irregular and shows a few staples, but no mass lesion is grossly noted at the margin. The margin is inked and the specimen is serially sectioned perpendicular to the margin at approximately 0.5-cm intervals. Two tumor masses are identified, measuring 2.0 x 1.6 x 1.0 cm and 0.8 x 0.8 x 0.5 cm. The masses are 1.2 cm apart, and the larger mass is present 0.5 cm from the closest surgical margin. No additional lesions are identified, and the uninvolved parenchyma is brown and appears noncirrhotic.

Section code

A1: Large mass in relation to surgical margin, perpendicular (frozen section)

A2: Smaller mass

A3: Random section of uninvolved liver

Total hepatectomy

Specimen is received in formalin and labeled “liver explant.” Upon removing the specimen from the container, a scan is performed for the presence of radioactivity. No abnormal radioactive signal is detected.

The liver weighs 1460 g and measures 19.0 x 15.0 x 12.5 cm. The specimen is oriented with the major landmarks. The liver is firm and the surface is diffusely nodular. No mass lesions are grossly apparent on the surface. The hilar structures identified, and after removal of the ligating sutures, the hepatic artery, portal vein,

and bile duct are noted to be patent. The hepatic veins are also patent. A 1.2 x 0.8 x 0.6 cm hilar lymph node is present. A 7.0 x 3.5 x 2.5 cm gallbladder is present in the gallbladder fossa and shows no external abnormalities. The included portion of cystic duct measures 1.5 cm in length and has been ligated at the margin of resection. A 0.8 x 0.5 x 0.5 cm cystic duct lymph node is present. On opening, the gallbladder contains mucoid greenish bile. No calculi or mucosal lesions are identified, and the wall is of normal thickness.

The liver is serially sectioned at approximately 0.5-cm intervals perpendicular to its long axis. The cut surfaces are diffusely nodular consistent with cirrhosis. Located in the right lobe is a 5.5 x 4.0 x 4.0 cm partly necrotic mass which spans the approximate junction of segments V and VIII. The grossly viable areas of the mass are fleshy with greyish to green appearance. On gross estimation approximately 50% tumor necrosis appears to be present; however, the necrosis appears to extend into the surrounding nontumorous parenchyma. A few large vessels are present adjacent to the mass; however, no vascular invasion is grossly evident. In the left lobe segment III an indeterminate nodule is present with a greenish yellow appearance. The nodule measures 1.5 x 1.5 x 1.0 cm and stands out in contrast to the background cirrhotic liver. No necrosis is apparent. No other lesions or masses are identified.

Section code

A1: Hilar vascular and biliary margins.
A2: Hilar lymph node
A3-A4: Random sections, right lobe
A5-A6: Random sections, left lobe
A7-A11: Right lobe mass
A12: Right lobe mass and adjacent vessel
A13-14: Left lobe mass
A15: Gallbladder and cystic duct margin

V. Common pathologic findings in liver specimens

Common neoplasms in liver specimens include metastatic carcinoma or sarcoma, primary malignancies (hepatocellular carcinoma, cholangiocarcinoma), and liver cell adenoma. Nonneoplastic lesions include cysts or cyst wall, focal nodular hyperplasia, hemangioma, and inflammatory lesions (complicated abscess, pseudotumors).

VI. Common potential pitfalls in tumor staging

The T category of staging for hepatocellular carcinomas is dependent on tumor size, number, and blood vessel invasion.

On gross examination of liver specimens, especially explants, it is important to sample any nodule that stands out against the cirrhotic nodular parenchyma. Grossly missed tumor nodules may lead to understaging.

Tumors that have been treated with embolization may be associated with necrosis of the surrounding benign liver parenchyma, and including such areas in measurements may incorrectly document a larger tumor size (Figure 15-6).

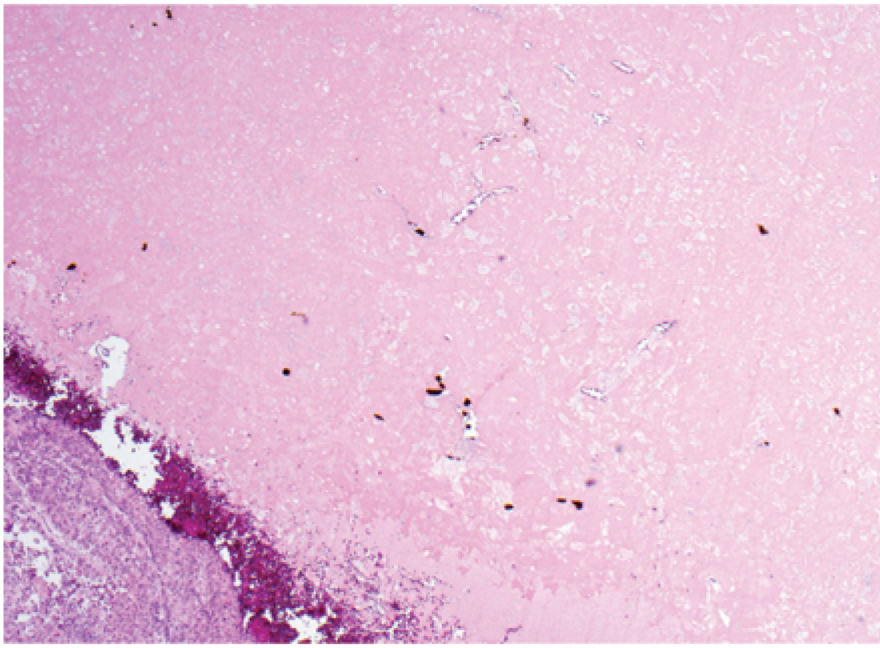
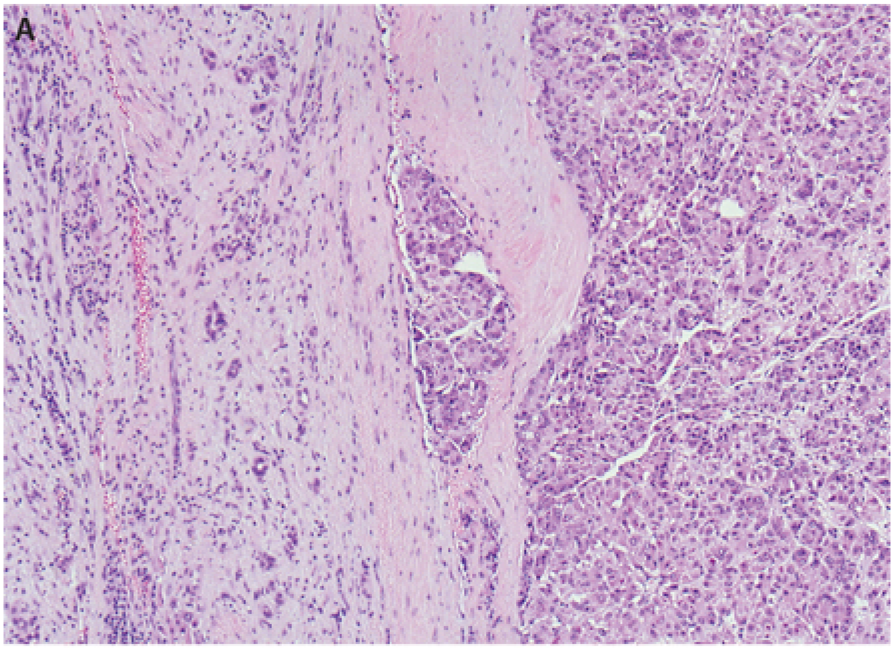


Figure 15-6. Hepatocellular carcinoma with necrosis secondary to radioembolization treatment. Presence of necrosis within and around the tumor may lead to overestimation of tumor size on gross examination (H&E stain; magnification x40).

If tumor is located close to major vascular structures, sectioning should include these structures to evaluate for tumor invasion. Major vessels included in the T4 category include the major branches of portal vein (right and left), hepatic veins (right, middle, left), or the main branches of the hepatic artery. Assessment for small vessel invasion is also important for pathologic staining and involves obtaining multiple sections of the tumor. One area of difficulty can be distinguishing vascular invasion from retraction artifact, and a CD31 immunostain may be helpful in this situation (Figure 15-7).



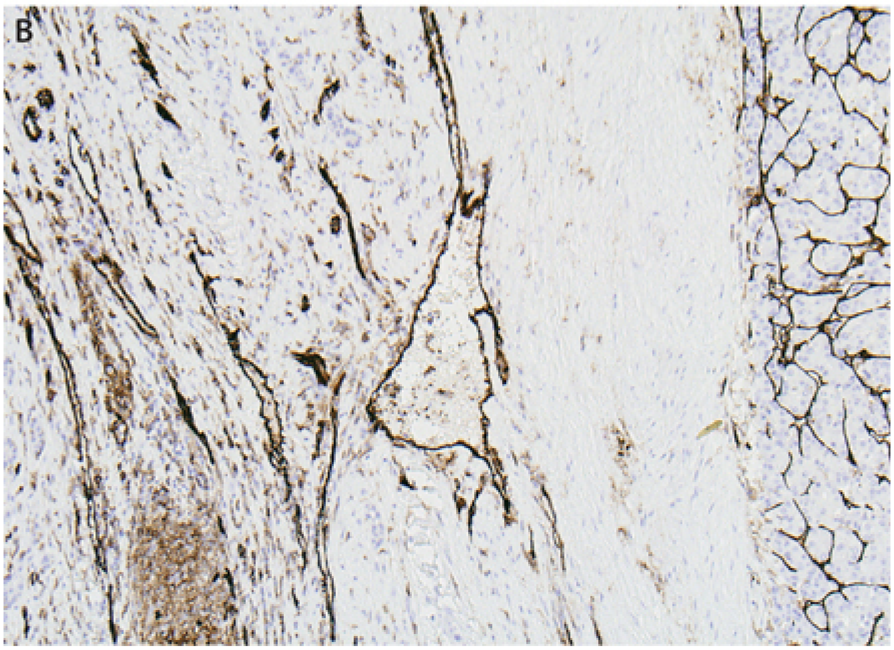


Figure 15-7. A. Small focus of tumor highly suspicious for vascular invasion by hepatocellular carcinoma (H&E stain, magnification x100). B. CD31 immunohistochemistry, showing the same area as in A. Tumor is absent on the deeper level, but the stain clearly highlights the vascular space.

Sample Report

Liver, right lobe, resection: Fibrolamellar carcinoma, forming a mass measuring 8.0 cm in greatest dimension. The margin of resection is uninvolved by tumor. The nonneoplastic adjacent liver parenchyma shows mild tumor-related changes including inflammation and fibrosis; however, no morphologic changes of background chronic liver disease are seen. Please refer to the cancer reporting protocol below.[7,8]

Procedure: Partial hepatectomy

Tumor Focality: Solitary

Tumor Site: Right lobe

Tumor Size:

Greatest dimension of viable tumor: 8.0 cm

Additional dimension: 7.0 x 5.5 cm

Treatment Effect: No known presurgical therapy

Histologic Type: Fibrolamellar carcinoma
Histologic Grade: G2: Moderately differentiated
Tumor Extension: Tumor confined to the liver
Parenchymal Margin: Uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin: 0.5 cm
Vascular Invasion: Not identified
Perineural invasion: Not identified
Regional Lymph Nodes: No lymph nodes submitted or found
Pathologic Stage Classification (pTNM, AJCC 8th Edition):
  Primary Tumor: pT1b: Solitary tumor >2 cm, without vascular invasion
  Regional Lymph Nodes: pNX: Regional lymph nodes cannot be assessed

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16. Intrahepatic Bile Ducts

Ashwini K Esnakula, MD, MS; Xiuli Liu, MD, PhD

Intrahepatic bile ducts constitute second order segmental bile ducts and proximal septal, and interlobular bile ducts of the biliary tree.[1] The tumors of intrahepatic bile ducts are diverse and include benign lesions, neoplasms such as mucinous cystic neoplasms and intraductal papillary neoplasms with associated risk of malignancy, and cholangiocarcinomas with poor outcome. Hence, diligent and meticulous handling of the resection specimen is essential for accurate diagnosis and staging which is helpful in guiding further management and prognosis.

The most common malignancy of intrahepatic bile ducts is cholangiocarcinoma. Intrahepatic cholangiocarcinoma (ICC) is the second most common malignancy of liver after hepatocellular carcinoma, with an overall incidence of 0.7 per 100, 000 adults in the United States.[2] Although the overall incidence of ICC is low, there has been steady increase in incidence over the past four decades.[3] The risk factors for ICC are similar to hepatocellular carcinoma and include primary sclerosing cholangitis, cirrhosis, chronic viral hepatitis, biliary lithiasis, and biliary parasitic infections. The overall prognosis of ICC is poor, with overall 5-year survival only up to 45%.[2,4]

The focus of this chapter is to provide guidance for appropriate handling of resection specimen for intrahepatic biliary lesions which is primarily partial hepatectomy specimen. The assessment of surgical margins during intraoperative consultation, gross examination, adequate sampling, and reporting of resection specimens using the College of American Pathologists (CAP) cancer protocol will be discussed.

I. Indications for resection

Benign bile duct adenoma and hamartoma are typically small, multiple, and subcapsular, and are usually identified as incidental lesions on imaging or laparoscopy. As these lesions mimic metastatic disease, they are frequently resected for intraoperative consultation.[5] Mucinous cystic neoplasm (MCN, also called hepatobiliary cystadenoma), premalignant neoplasms, typically are large lesions and commonly present with pain and abdominal mass. Another premalignant neoplasm, intraductal papillary neoplasm of bile ducts (IPNB, so called biliary papilloma/papillomatosis), can be multifocal and diffuse and present with obstructive jaundice. Both MCN and IPNB can develop invasive carcinoma and hence these lesions are resected.[6] ICCs usually develop as large mass at the periphery of the liver, and they present with nonspecific symptoms such as abdominal pain and weight loss. Rarely, these patients can present with jaundice when the tumor involves a hepatic duct. Currently, surgical resection is the only curative option for ICC. However, most patients present with locally advanced or metastatic disease at the time of diagnosis, and only 15% of the patients are amenable for complete resection at the time of diagnosis.[4] Partial hepatic resection including segmental resection or lobectomy is the procedure of choice to achieve complete resection of intrahepatic bile duct tumors. Segmental resection of liver is based on eight functional segments of liver as lineated by vascular supply and biliary drainage.[7] Total hepatectomy with orthotopic liver transplantation for ICC is controversial and usually contraindicated at many transplant centers.[8]

II. What to expect grossly and microscopically

Benign cysts such as solitary bile duct cysts are usually small unilocular cysts and histologically show single layer of columnar or cuboidal type biliary epithelium.[9] Bile duct hamartomas (Von Meyenburg complex) are usually multiple, irregular, subcapsular, tan-white lesions (Figure 16-1A). Histologically, they are composed of irregular and varying sized dilated bile ducts with or without intraluminal bile in a background of hyalinized stroma (Figure 16-1B). These bile ducts are lined by benign cuboidal epithelium. Bile duct adenomas (peribiliary gland hamartoma) are small, round, subcapsular, tan-white lesions. Histologically, they are well circumscribed but unencapsulated and composed of small round glands with benign cuboidal epithelium in a background of variable fibrous stroma. They lack irregular dilated ducts or intraluminal bile, which can be helpful in differentiating these from bile duct hamartomas. Bile duct adenomas and hamartomas are frequently

encountered during intraoperative consultation as they mimic metastatic disease. The above gross and microscopic features are helpful in distinguishing these from metastatic tumor deposits.[5,6]

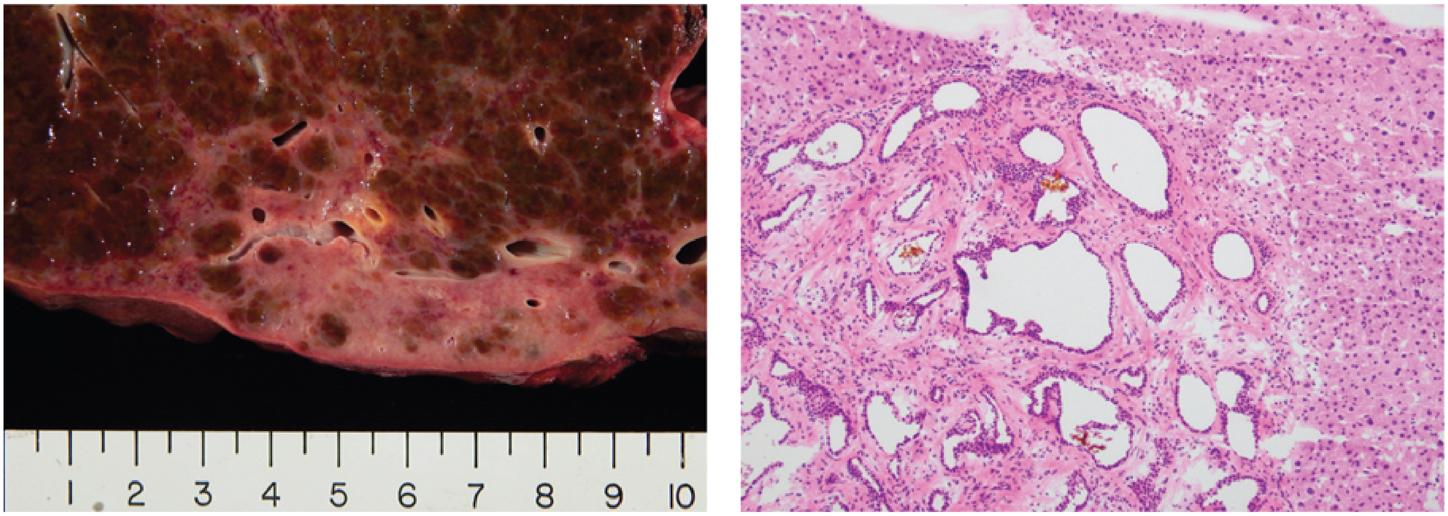

Figure 16-1. Bile duct hamartoma. A. Partial hepatectomy specimen. There is an irregular subcapsular tan-white tumor. B. Frozen section slide of this tan-white subcapsular lesion reveals dilated irregular bile ducts with luminal bile and lined by benign cuboidal epithelium that is consistent with a bile duct hamartoma.

MCNs of the liver are grossly and microscopically similar to the pancreatic MCNs. They are typically mucin-filled, large, complex, cystic lesion with thick cyst wall and septae (Figure 16-2A). The benign neoplasms usually show smooth lining and histologically show a simple columnar epithelium with mucinous cytoplasm and minimal cytological atypia. These lesions show variable amount of characteristic bland subepithelial spindle cell stroma resembling the ovarian stroma (Figure 16-2B). Based on cytologic atypia, these can be further classified as low-, intermediate-, and high-grade dysplasia (Figure 16-2C). Grossly, the presence of papillary excrescences and mass lesion in the cyst wall is worrisome for malignant transformation. Such areas should be extensively sampled to confirm or exclude the possibility of an underlying malignancy.[6,10]

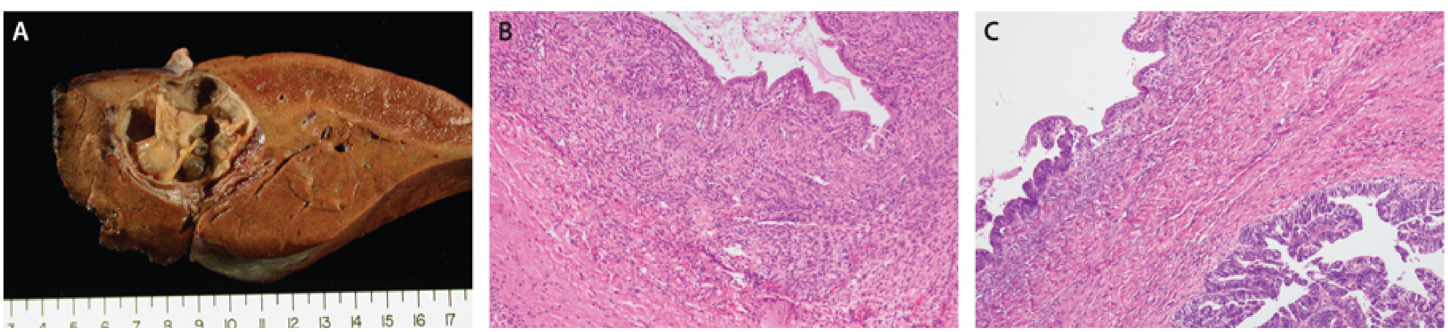

Figure 16-2. Mucinous cystic neoplasms of the liver. A. Partial hepatectomy specimen. There is a complex cystic mass with thick capsule. The inner lining is smooth and shiny without any evidence of papillary excrescences or mass lesions. B. Histologically, the cyst wall shows a single layer of low-grade columnar epithelium with an underlying ovarian-type stroma. C. This microscopic image of another cystic neoplasm with associated mass lesion showing areas of low-grade and high-grade mucinous cystic neoplasm and underlying invasive adenocarcinoma (not shown in this image).

ICC constitutes adenocarcinoma arising anywhere from peripheral ductules to segmental bile ducts. Distinction between extrahepatic and intrahepatic cholangiocarcinoma at times can be challenging, especially when an intrahepatic tumor extends to involve the hilum.[1] Thorough gross assessment of the tumor to identify the epicenter can be helpful to make this distinction. Based on the growth pattern, the ICCs can be classified into three subtypes: (1) mass forming type, (2) periductal infiltrating type, and (3) mixed type. Mass forming

type is the most common type and characterized by radial infiltrating growth pattern into the adjacent hepatic parenchyma leading to a mass lesion. Grossly, these tumors are gray-white, firm, and well delineated from the adjacent hepatic parenchyma. Periductal infiltrating type is characterized by longitudinal growth along the bile ducts without mass formation and typically an ill-defined irregular tan-white lesion along the course of bile ducts (Figure 16-3A,B). The mixed type shows both mass-forming and periductal infiltrating growth patterns.[1,11] The prognostic significance of these subtypes is controversial, although initial studies showed that periductal infiltrating type is associated with poor prognosis; however, the recent evidence suggests a relative favorable prognosis.[12,13] Typical histologic findings of ICC are of adenocarcinoma characterized by infiltrating malignant glands in a background of desmoplasia. Similar to extrahepatic cholangiocarcinoma, ICC can be associated with a mass-forming precursor lesion IPNB or a non–mass-forming precursor biliary intraepithelial neoplasia (BilIN). In IPNB, intrahepatic bile ducts are dilated and the lumen can be completed occluded by intraductal tumor (Figure 16-4A). Histologically, IPNB consists predominantly of papillary structures with fine fibrovascular cores covered by biliary epithelial cells (Figure 16-4B). Some IPNB may give rise to an invasive ICC (Figure 16-4B). IPNB and BilIN are further discussed in detail in chapter 11, Distal Extrahepatic Bile Ducts. Recently, two distinct histologic subtypes of ICCs, small duct type and large duct type, have been proposed,[14] but this subtyping is currently not required for the CAP protocol. Rarely, certain tumors show both gross and histologic features of hepatocellular carcinoma and cholangiocarcinoma, and are regarded as combined hepatocellular-cholangiocarcinoma (mixed hepatocholangiocarcinoma) (Figure 16-5A,B). These tumors are also staged according to the American Joint Committee on Cancer (AJCC) staging system for ICC.[1]

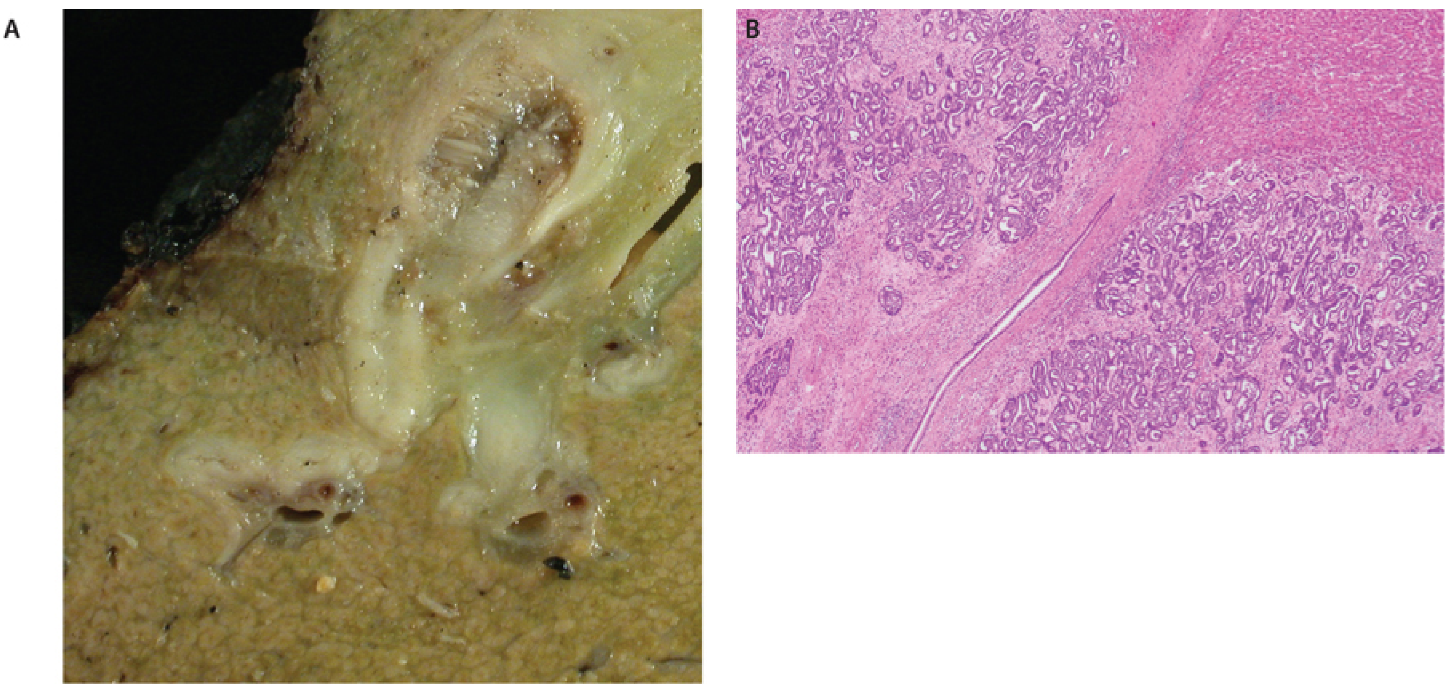

Figure 16-3. Intrahepatic cholangiocarcinoma of periductal infiltrating type. A. Partial hepatectomy specimen. The liver is extensively involved by large multinodular white firm mass. Focally, the tumor shows areas of periductal infiltrating pattern. Tumor grossly extends to the inked resection margin. B. Histologically, this tumor shows a periductal infiltration growth pattern characterized by infiltrating adenocarcinoma along the central benign segmental bile duct.

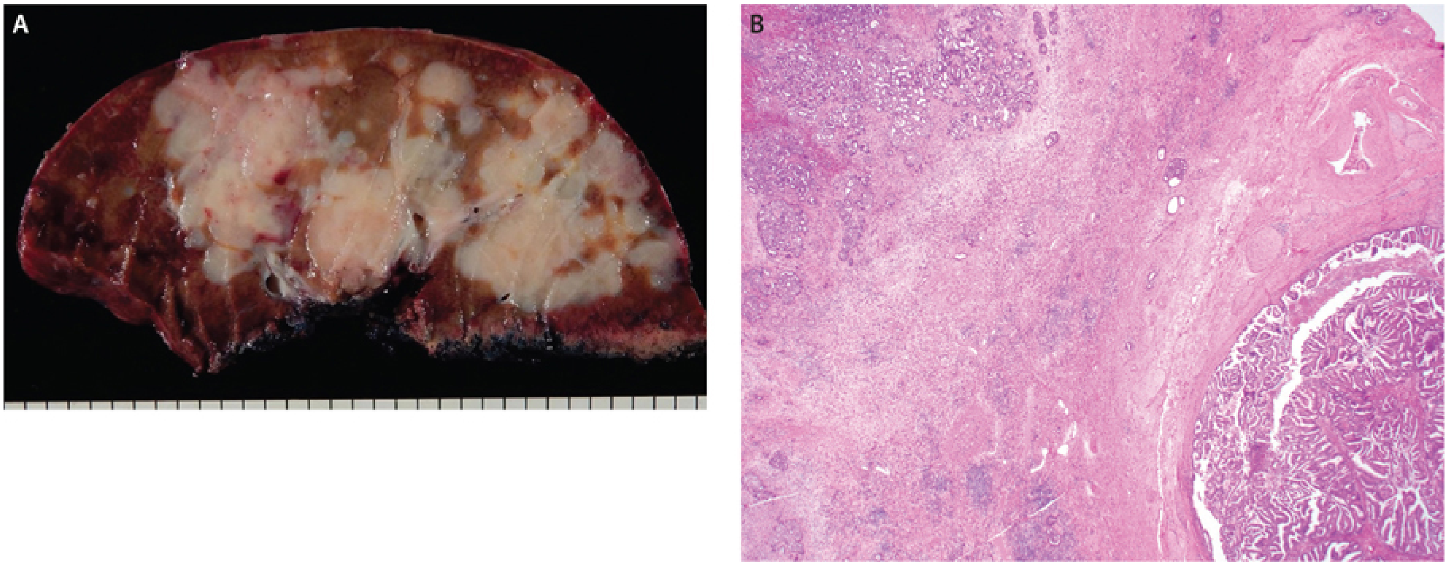

Figure 16-4. Intraductal papillary neoplasm of bile ducts (IPNB). A. Partial hepatectomy specimen. Intrahepatic bile ducts are dilated and the lumen is completed occluded by intraductal tumor. B. Histologically, the intraductal tumor is composed of papillary proliferation of biliary epithelium. An associated intrahepatic cholangiocarcinoma is also present.

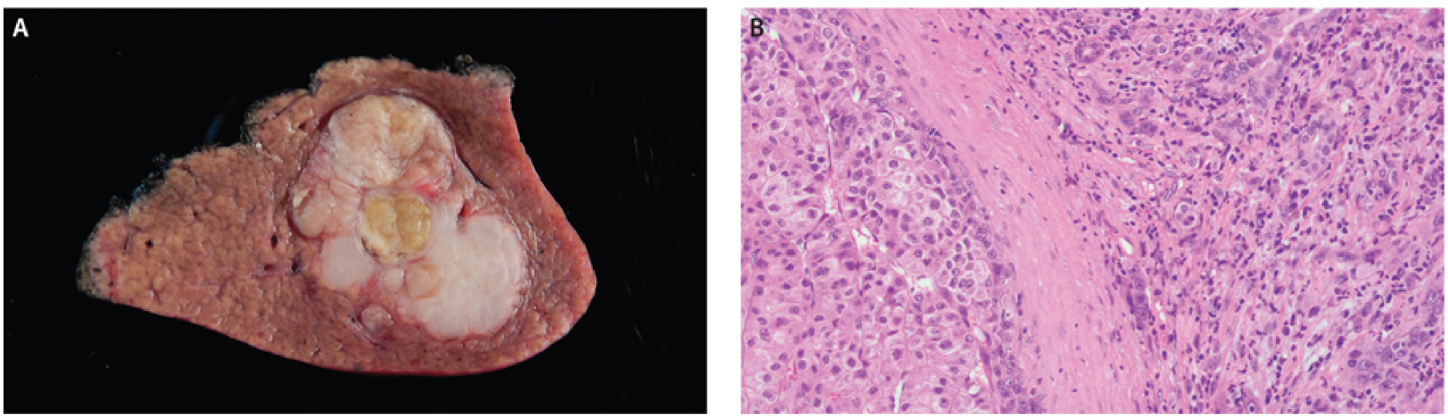

Figure 16-5. Combined hepatocellular and cholangiocarcinoma. A. Partial hepatectomy specimen. The liver is involved by a large variegated mass with white firm areas and tan-yellow areas. B. Histologically, the tumor is consistent with a combined hepatocellular and cholangiocarcinoma The tumor shows classic, moderately differentiated hepatocellular carcinoma on the left characterized by atypical hepatocytes in large trabecular architecture. On the right is a poorly differentiated cholangiocarcinoma characterized by infiltrating nests, cords, rare glands of highly pleomorphic tumor cells. These findings are consistent with a combined hepatocellular and cholangiocarcinoma.

III. Dissection techniques

Partial hepatectomy (lobectomy/segmentectomy)

1. Orient the specimen. Surgical information provided by the surgeon or the operative note or radiographic study regarding the segments resected will be helpful with orientation.
2. Describe the external surface and capsule adjacent to the tumor (puckered, disrupted, nodular).
3. Identify resected hilar structures (portal vein, bile ducts, and hepatic arteries) if the resection includes the hilum and mark the parenchymal resection margin with ink. Note a segment of inferior vena cava may be attached along the caudate lobe. En face sections of vascular and bile duct margin should be submitted.
4. Section the specimen perpendicular to the parenchymal resection margin, usually in the axial plane.
5. Section at <0.5-cm intervals in order to visualize all tumor nodules.
6. Record the number, size, shape, color, and consistency of the tumor(s) and measure the closest distance from the hilum if applicable, resection margins, and capsule surface.
7. Evaluate the vessels and bile ducts for gross involvement by the tumor.

8. If frozen section evaluation of the resection margins is requested, submit the perpendicular section of the closest margin in relation to tumor.

9. Collect fresh tissue for tissue banking (if applicable) following institutional and protocol guidelines.

10. Specimen should be fixed overnight after the initial preparation and examination.

11. Submit at least one section per centimeter of the tumor and include sections of the tumor(s) with relationships to adjacent vessels, bile ducts, capsule, and hepatic parenchyma.

12. For suspected mucinous cystic neoplasms, consider submitting the entire cyst wall if possible, at least submitting the entire papillary excrescences or mass lesions to evaluate for invasive carcinoma.

13. If premalignant tumors such as IPNB are suspected, submit the tumor entirely to evaluate for invasive carcinoma.

14. Submit at least one representative section of the uninvolved liver.

15. If a gallbladder is present with the specimen, evaluate for involvement by the tumor.

16. Evaluate for the presence of lymph node at the hilar region, if applicable.

IV. Gross descriptions

Partial Hepatectomy (Lobectomy)

The specimen consists of a 350 g, 11.5 x 8 x 5 cm lobectomy specimen consisting of left lobe of liver. The external surface is intact and smooth. The resection margin with cautery artifact measures 6 x 5 cm and is inked black. The vessels and ducts at the margin are patent and without any gross involvement by the tumor. Serial sectioning reveals a single 5.5 x 4.3 x 4 cm tan-white, firm mass involving the segments 2 and 3. The tumor is present at 1.5 cm from the parenchymal margin, 2 cm from the capsule, and 3 cm from the nearest vascular and ductal margin. The uninvolved liver parenchyma is uniformly brown and unremarkable. Representative sections are submitted as follows: A1-2 Tumor in relation to nearest parenchymal margin, perpendicular sections; A3 Bile duct and vessels at margin, en face; A4-6 Tumor; A7 Tumor in relation to adjacent parenchyma; A8 Uninvolved hepatic parenchyma.

V. Common potential pitfalls and solutions

Bile duct hamartomas and adenomas are the most common subcapsular lesions submitted during intraoperative consultation to rule out metastatic carcinoma. Careful gross and microscopic evaluation of these lesions is helpful in excluding metastatic carcinoma. IPNB and MCN are commonly associated with invasive adenocarcinoma, hence when suspected careful gross examination with extensive sampling of these lesions is recommended. In cases of intrahepatic cholangiocarcinoma, the bile ducts at the margin should be sampled to exclude the possibility of premalignant lesions such as IPNB and BilIN.

VI. What to include in the report

The report of the specimens with diagnosis of malignancy of intrahepatic bile ducts should contain the required elements in the CAP cancer protocol, which includes pathologic TNM requirements from the 8th edition AJCC staging manual.[15] This protocol is applicable for intrahepatic cholangiocarcinoma, invasive carcinomas arising in a background of IPNB and MCN, combined hepatocellular-cholangiocarcinoma, small cell and large cell (poorly differentiated) neuroendocrine carcinoma. Currently, the size of the tumor defines T1 category. Multifocality or intrahepatic vascular invasion constitutes T2. Visceral peritoneal invasion and adjacent organ involvement constitutes T3 and T4, respectively.[1] In addition to the required elements, the report should also convey information that may not be included in the cancer protocols and also provide clarification to problematic or complex diagnoses including any ancillary studies that are performed. Often, the “top line diagnosis” can be used to elaborate on the summarized findings in the synoptic report. In addition, the synoptic report is by definition a summary of the entire case.

An example utilizing both the “top line diagnosis” and the CAP cancer protocol for a liver lobectomy resection.

Final Diagnosis

LIVER, LEFT LOBE, LOBECTOMY: MODERATELY DIFFERENTIATED INTRAHEPATIC CHOLANGIOCARICNOMA, 5.5 CM (See synoptic report/CAP protocol)

Tumor confined to hepatic parenchyma

Lymphovascular invasion is not identified

All margins are negative for invasive carcinoma and high-grade intraepithelial neoplasia

Synoptic Report

Procedure: Partial hepatectomy

Tumor Size: Greatest dimension – 5.5 cm

Tumor Focality: Solitary, segments 2 and 3

Histologic Type: Intrahepatic cholangiocarcinoma

Histologic Grade: G2: Moderately differentiated

Tumor Growth Pattern: Mass-forming

Tumor Extension: Tumor confined to hepatic parenchyma

Margins:

Hepatic Parenchymal Margin: Uninvolved by invasive carcinoma

Distance of invasive carcinoma from margin: 1.5 cm

Bile Duct Margin: Uninvolved by invasive carcinoma and high-grade intraepithelial neoplasia

Distance of invasive carcinoma from margin: 3 cm

Lymphovascular Invasion: Not identified

Perineural Invasion: Not identified

Regional Lymph Nodes: No lymph nodes submitted or found

Pathologic Stage Classification:

TNM Descriptors: Not applicable

Primary Tumor (pT): pT1b: Solitary tumor >5 cm without vascular invasion

Regional Lymph Nodes (pN): pNX: Regional lymph nodes cannot be assessed

Distant Metastasis (pM): Not applicable

Additional Pathologic Findings: None

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17. Pancreas

Huamin Wang, MD, PhD; Volkan Adsay, MD; Jian He, MD, PhD

Exocrine and endocrine neoplasms

Pancreatic resection specimens are rare in daily practice, especially for community-based practicing pathologists. These specimens are often difficult to be orientated for correct identification of margins and the relationship of tumor with adjacent anatomic structures. In addition, there is no universally accepted standard protocol for gross examination and sampling of pancreatic resection specimen. Therefore, there are significant variations in reporting the margin status, yield of regional lymph nodes, misclassification of tumor stage, and incomplete pathologic reporting, etc.

There are six major types of resection for pancreatic neoplasms: (1) pancreaticoduodenectomy (Whipple procedure), which includes the head and neck of the pancreas, distal stomach, duodenum, and proximal jejunum; (2) pylorus-sparing pancreaticoduodenectomy, which includes the head and neck of the pancreas, duodenum, and proximal jejunum; (3) total pancreatectomy; (4) distal pancreatectomy with or without splenectomy; (5) partial/segmental pancreas resection; and (6) enucleation of the pancreatic neoplasm. Although pancreaticoduodenectomy is performed mainly for the resection of primary neoplasms of the pancreas, it is also often performed for the resection of primary duodenal neoplasms in the periampullary region, primary carcinomas of common bile duct, or neoplasms of the ampulla of Vater. Proper handling and careful gross and histologic examination of the pancreatic resection specimens are the key for determining the primary site (pancreatic vs ampullary vs nonampullary duodenal vs common bile duct) in pancreaticoduodenectomy specimens, accessing the margin status, accurate diagnosis, and staging, and assessing treatment effect if patient had received neoadjuvant therapies. For cases in which resection of superior mesenteric vein/portal vein (SMV/PV) was performed, gross identification and proper sampling of the resected portion/segment of SMV/PV is critical to determine the margins status and involvement of the vein. Accurate pathologic diagnosis, staging, tumor grading, comprehensive pathologic evaluation, and reporting using the cancer protocol for pancreatic exocrine and endocrine neoplasms from the College of American Pathologists (CAP) have been shown to be the major prognostic factors for patients with pancreatic neoplasms and serve as the foundation for the planning of postsurgical management of these patients.

In this chapter, we will focus on the appropriate handling and identification of the margins, intraoperative consultation/frozen section diagnosis, gross examination of different type of pancreatic resection specimens, sampling schemes, histopathologic evaluation and synoptic reporting of pancreatic resection specimens using the CAP protocols for pancreatic exocrine and endocrine neoplasms.

I. Indications for different types of pancreatic resections

Pancreaticoduodenectomy and pylorus-sparing pancreaticoduodenectomy: These types of surgeries are mainly performed for primary neoplasms located in the head or neck region of the pancreas, primary duodenal neoplasms in the periampullary region, primary carcinomas of distal/intrapancreatic common bile duct, or neoplasms of the ampulla of Vater. Preservation of the pylorus in pancreaticoduodenectomy may improve the long-term gastrointestinal function, such as less frequent peptic ulcers and dumping syndrome.[1] Total pancreatectomy is indicated for patients with more curable conditions including multicentric neuroendocrine tumors, intraductal papillary mucinous neoplasm with diffuse ductal involvement or invasive carcinoma, for patients with familial pancreatic cancer and high-grade premalignant lesions, and rarely for patients with chronic pancreatitis and intractable pain.[2]

Distal pancreatectomy with or without splenectomy is indicated for pancreatic neoplasms located in the body or tail of pancreas. Segmental pancreas resection and enucleation are only used very selectively to treat small indolent neoplasms such as cystic lesions or small well-differentiated pancreatic neuroendocrine tumors.

II. Specimen orientation, identification, and evaluation of the margins in pancreaticoduodenectomy and total pancreatectomy specimens

1. Specimen orientation and identification of the margins: There are five standard resection margins in a pancreaticoduodenectomy specimen. These margins include the pancreatic parenchymal margin, common bile duct (CBD) margin, and retroperitoneal margin, the latter also referred to as superior mesenteric artery (SMA) or uncinate margin. Proximal duodenal/gastric and distal jejunal margins are also sampled as a part of the routine protocol. For total pancreatectomy specimens, there is no pancreatic parenchymal resection margin. The anterior surface, posterior surface, and SMV/PV groove are not considered as resection margin in the current CAP protocol and the American Joint Committee for Cancer (AJCC) staging manual, 8th edition.[3] However, the current CAP protocol recommends to ink the SMV/PV groove and to submit representative section(s) of the tumor at its closest approach to this surface. Reporting of tumor involvement of anterior and posterior surfaces is also recommended but not required. It should be noted here that some authors regard the posterior free surface and even the vascular/groove area as a part of the "posterior/retroperitoneal margin," which is hotly debated.

Proximal gastric or duodenal margin and distal jejunal resection margin are easy to identify; however, gross identification of the other three margins on the head of pancreas can be very difficult. To identify these three margins on the head of pancreas, we found the following two approaches to ease things greatly.

- Three-finger technique of the left hand: The pancreaticoduodenectomy specimen is laid on grossing board in such a way that proximal gastric/duodenal margin is pointing away from the grossing person, distal jejunal margin is point to him/her, and the head of pancreas is lying on top of the duodenum (Figure 17-1A). This will give the grossing person a direct view from the posterior aspect of pancreatic head. From this view, the SMV/PV groove can be easily identified as a curved (concave, smooth surfaced) indentation between the neck and uncinated process of pancreas. This vascular bed corresponds to the mesenteric/portal vein that had been stripped off from the pancreas. The grossing person puts his/her left index finger in the SMV/PV groove, then uses the left thumb, index finger, and middle finger to grab the head of pancreas. The ovoid flat-surfaced edge, often cauterized, held between the index and middle fingers will be pancreatic parenchymal margin; the nonperitonealized, irregular, soft tissue edge held between the index finger and thumb will be the retroperitoneal margin; and the CBD margin will be located at the soft tissue edge on the right side where the index finger pointed to (Figure 17-1A).
- For the second approach, the duodenum is laid on the grossing board with the long arm of the duodenum towards the right and the stomach or short arm of duodenum to the left. When the pancreatic head is held suspended on the duodenum, a trapezoid-shaped view is readily identifiable (Figure 17-1B). The center of this trapezoid is the SMV/PV groove. To the left of SMV/PV groove will be the pancreatic parenchymal margin. To the right-outer edge of the trapezoid will be the retroperitoneal (uncinated/SMA) margin, which appears as fat-rich convex lumpy-bumpy, irregular surfaces.[4] When this retroperitoneal margin is followed to the top, the CBD margin will be located at the top right edge of the trapezoid (Figure 17-1B).

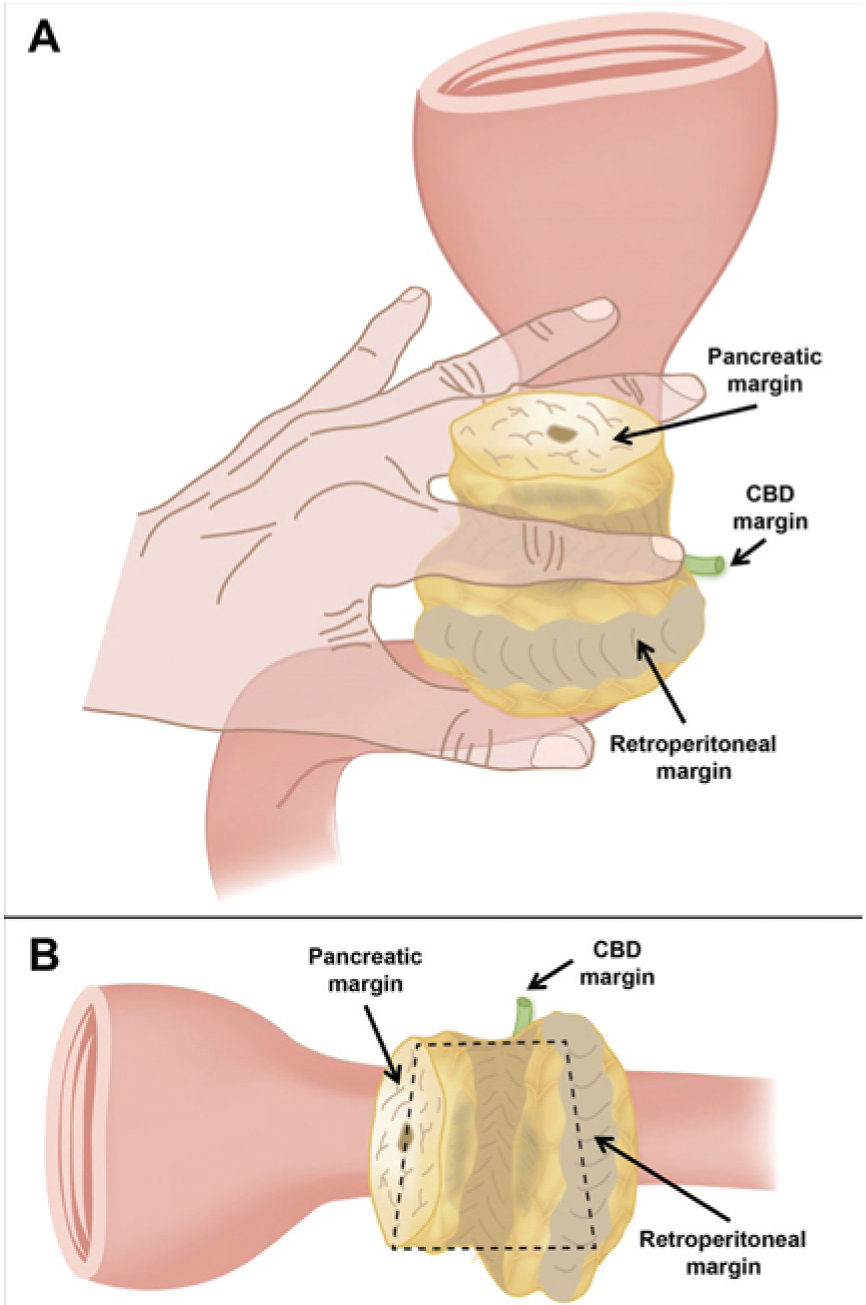

Figure 17-1. Identification of the pancreatic margin, common bile duct margin, and retroperitoneal (SMA or uncinate) margin in pancreaticoduodenectomy specimens using the three-finger approach (A) and the trapezoid approach (B).

Once identified, the pancreatic and bile duct margins should be entirely submitted en face for frozen section diagnosis and retroperitoneal margin should be inked with a reliable color.

2. Indications for frozen sections

Intraoperative frozen sections for pancreatic parenchymal and CBD margins are routinely performed in most institutions during pancreaticoduodenectomy. However, some recent studies failed to show the survival benefit of performing additional pancreatic resection in patients with pancreatic ductal adenocarcinoma if the original frozen section on pancreatic parenchymal margin is positive for carcinoma.[5] For CBD margin, however, obtaining additional bile duct resection may have merit, and thus it is justifiable to perform frozen sections in cases with carcinoma possible to be close to CBD margin (especially for CBD or ampullary carcinomas that can extend to this margin). Similarly, frozen sections of pancreatic margins are also justifiable for tumors with more indolent behavior such as intraductal papillary mucinous neoplasms (IPMNs), colloid carcinomas, and neuroendocrine tumors.

Retroperitoneal margin represents the nonperitonealized soft tissue cutting surface that is carefully dissected from the SMA. This margin is considered final once pancreaticoduodenectomy specimen is out since no additional tissue can be obtained by the surgeons and thus a frozen section does not alter the course of the operation. Therefore, we do not recommend frozen sections on retroperitoneal (uncinate/SMA) margin.

3. Sampling of the margins

For CBD and pancreatic parenchyamal margins, it is recommended to examine these margins in their entirety especially considering that these are small regions and this can be achieved in only one or two blocks. Most authors advocate to analyze these two margins as shave/en face, although some prefer to perform perpendicular sectioning of pancreatic parenchymal margin. We prefer the shave/en face approach but also advocate the submission of the immediately next slice for microscopic examination as well so that any uncertain findings at this true margin (which often shows crush/cautery artefact as well) can be verified by the findings in the adjacent tissue. This may also allow the reconstruction of the distance from the margin at the microscopic level in some cases.

For retroperitoneal (uncinate/SMA) margin, most authors agree on the perpendicular margin, and most also agree total submission of this region because this is the region where grossly unappreciated carcinoma elements can be discovered infiltrating very close to the margin due to the adipose-rich nature of this region and/or perineural invasion, whereas in other areas like vascular bed and posterior free surface, tumors often manifest as erosions, puckering, or nodularity that are grossly noticeable and thus can be sampled selectively. It should be noted here that some authors advocate total submission of not only the uncinate but also the posterior free surface as well as the SMV/PV groove as a part of the "posterior/RPM/uncinate/SMA" margin.[6] We do not use this approach because posterior free surface is not a true margin in the sense that the surgeons do not dissect it, and there is nothing they can do about it (it peels off readily), and furthermore, we also believe, if this region is to be regarded as a true "margin," then so should the anterior surface be. Interestingly, the schools that regard the posterior free surface a "margin" do not regard anterior surface a margin, which, in our opinion is a contradiction and is inaccurate. Additionally, submitting all these surfaces as perpendicular margin requires numerous more sections, which becomes unreasonable considering the cost-benefit ratio (the information gained has not been proven to have justifiable significance) unless it is in research setting.

4. Reporting of the pancreatic and CBD margins

The pancreatic and bile duct margins should be reported as negative or positive for carcinoma or high-grade dysplasia ("carcinoma in-situ"). In a patient with IPMN, if low-grade gastric-type epithelium is encountered at the margins, it may be advisable to report it as "low-grade mucinous epithelium present, either low-grade IPMN or low-grade PanIN [pancreatic intraepithelial neoplasia], negative for high-grade dysplasia or invasive carcinoma," which is believed not to warrant any additional operation unless there is more abnormality in the remaining pancreas or there are exuberant papilla formation or the cells are intestinal or oncocytic type. In a patient with pancreatic ductal adenocarcinoma (PDAC), there is no need to report low-grade dysplasia (PanIN1 and PanIN2) on the pancreatic resection margin, but if there is convincing high-grade PanIN or carcinoma in situ, that should be reported. Additional pancreatic parenchymal margin is not recommended if only low-grade dysplasia is present at pancreatic margin at the time of frozen section.[7] Same is also believed to be the case for CBD margin (BilIN-3/CIS warrants proper documentation).

III. Tumor size measurement

In the current AJCC staging system, the pathologic tumor (pT) stage of both pancreatic exocrine and endocrine tumors are formulated based on the tumor size in the greatest dimension.[3] For pancreatic exocrine tumor, the pT is classified as follows: pT1 tumor ≤2 cm (subdivided into pT1a tumor ≤0.5 cm, pT1b tumor >0.5 cm and <1 cm, and pT1c tumor ≥1 cm and ≤2 cm), pT2 tumor >2 cm and ≤4 cm, pT3 tumor >4 cm. The criteria for pT4 tumor is defined as tumor involving the celiac axis, superior mesenteric artery and/or common hepatic artery, irrespective of tumor size,[3] which is surgically unresectable. Tumor size is determined by measurement of the gross lesion and should be corroborated with the microscopic assessment. For an invasive carcinoma arising in an intraductal papillary mucinous neoplasm (IPMN), intraductal tubulopapillary neoplasm (ITPN) or

mucinous cystic neoplasm (MCN), only the size of invasive carcinoma should be used to determine the T category. If invasive carcinomas arising in association with an IPMN, ITPN, or MCN are multifocal, the size of the largest focus as well as cumulative size of all invasive carcinoma foci should be included in the report. Currently, similar to the breast, the convention seems to be that the T category is determined based on the size of largest focus of invasive carcinoma based on the current CAP protocol. However, it is debatable as to whether the largest focus is the only determinant of clinical outcome. There is evidence even in breast that in fact summation of all the invasive tumor sizes may reflect tumor behavior better.[8,9]

Tumor size measurement is often straightforward for pancreatic neuroendocrine tumors, but it can be quite challenging for PDACs, which are by definition ill-defined tumors. This becomes even more problematic in cases that have been treated with neoadjuvant chemotherapy and/or radiation therapy since neoadjuvant therapy often leads to marked fibrosis, which typically involves both tumor and adjacent nonneoplastic pancreatic parenchyma. Systemic approaches that combine gross measurement of the possible tumor area and sequential continuous mapping sections across the largest dimension of the possible tumor area with adjacent pancreas/soft tissue and/or adjacent organ(s) for microscopic validation is critical to accurately measure tumor size and to assign the correct ypT category (Figure 17-2). If there is no grossly identifiable tumor after neoadjuvant therapy, we would recommend systemically submitting the entire resected portion of the pancreas, common bile duct, and ampulla of Vater to rule out microscopic foci of residual carcinoma. When multiple foci of viable tumor present in the same treated tumor bed/mass, the tumor size can be measured using the method for the standardized pathologic evaluation of postneoadjuvant specimens of breast cancer by an international working group[10] and a recent study on treated pancreatic ductal adenocarcinoma as illustrated in Figure 17-3.[11] Alternatively the tumor size can be measured as a sum of the maximal linear dimensions of all separate foci of residual viable tumor for ypT staging. Sizable acellular mucin pools after chemoradiation, if present, should not be interpreted as residual tumor.

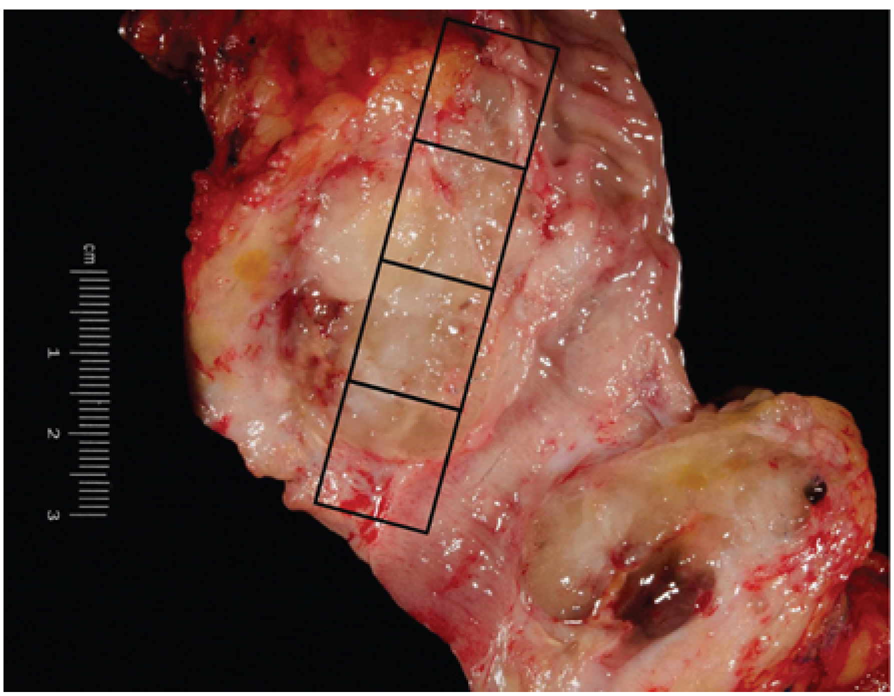

Figure 17-2. Sequential continuous sections across the largest dimension of the possible tumor area with adjacent pancreas/soft tissue and/or adjacent organ(s) to validate the tumor size measurement microscopically for accurate assignment of pathologic tumor (pT) stage.

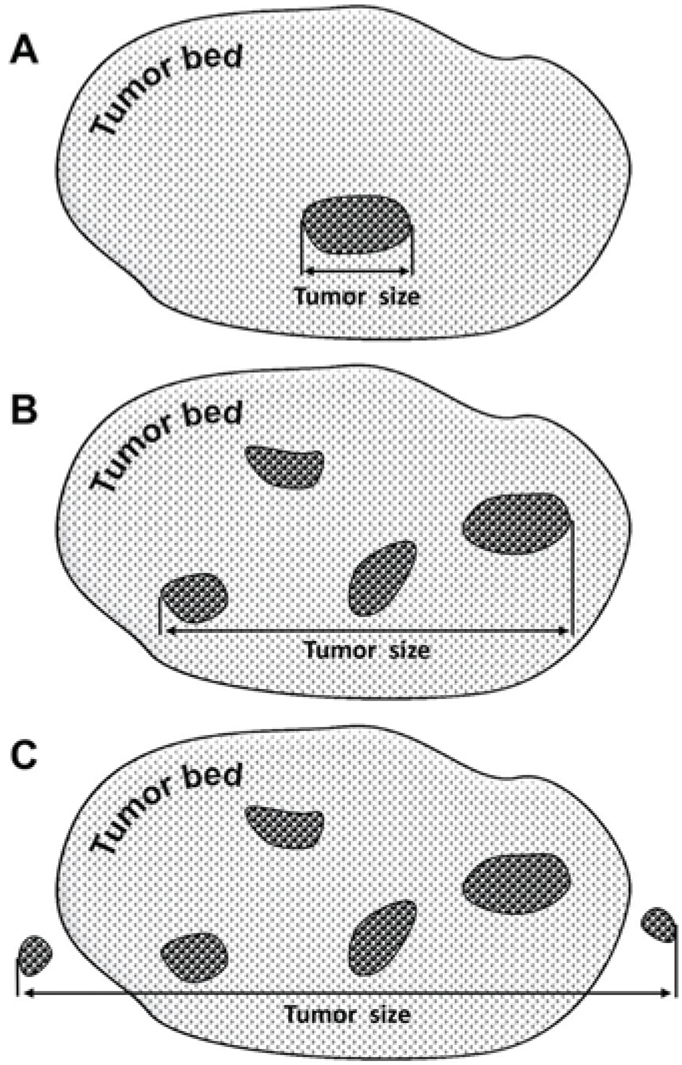

Figure 17-3. Schematic illustration of the tumor size measurement in pancreatic resection specimens after treated with neoadjuvant therapy. If only a single focus of viable residual tumor is present, the largest linear dimension of the viable tumor focus on H&E slide should be used as the final tumor size (A). When more than one microscopic foci (multifocal) of viable residual tumor are present, the largest linear dimension of the area involved by all islands of viable residual tumor including the intervening stroma should be used as the residual tumor size (B). If viable residual tumor invades the pancreas and/or soft tissue beyond the tumor bed area, the largest dimension of the entire area involved by all islands of viable residual tumor should be used as the final tumor size (C).

IV. Tissue banking

If there is an institution tissue bank protocol and/or a research protocol requesting for tissue samples, typically the tumor, adjacent normal pancreas, and small bowel mucosa should be harvested for these protocols based on the gross evaluation. Frozen sections to validate the histology of the harvested tissue may be performed as requested. Tissue harvesting and processing of the harvested tissue samples should be performed according to the institutional tumor bank guidelines and the corresponding research protocol. Best effort from pathology should be made to harvest tissue as soon as possible, which minimizes the ischemia time for better quality of the banked tissue.

V. Grossing of pancreatectomy specimens

1. Grossing of pancreaticoduodenectomy and total pancreatectomy specimens

a. Describe all components in the specimen and measure the size of each component.

b. Identify all margins and ink the retroperitoneal margin as described above. Submit sections for frozen diagnosis if requested by the surgeon.

c. The SMV/PV resection can be either a patch resection or a segmental resection. Carefully inspect SMV/PV groove to search for possible vein wall or segment of SMV/PV from vein resection. Tumor invasion into the tunica adventitia, tunica media or intima, or lumen of the resected SMV/PV was a poor prognostic factor for survival in patients with pancreatic ductal adenocarcinoma.[12] For patch resection of the vein, measure size of the vein wall, ink the peripheral vein resection margin, then submit the tips of the vein wall (ink side down) and the rest portion of the vein and perpendicular vein margin with underlying tumor in a fashion similar to a skin ellipse (Figure 17-4A). For segmental vein resection, measure the length and diameter of the vein, submit the superior and inferior vein margins en face and the rest of the resection segment of SMV/PV with underlying tumor. This should be done after overnight fixation and great care should be made to take only a thin rim of the superior and inferior vein margins for en face sections (Figure 17-4B).

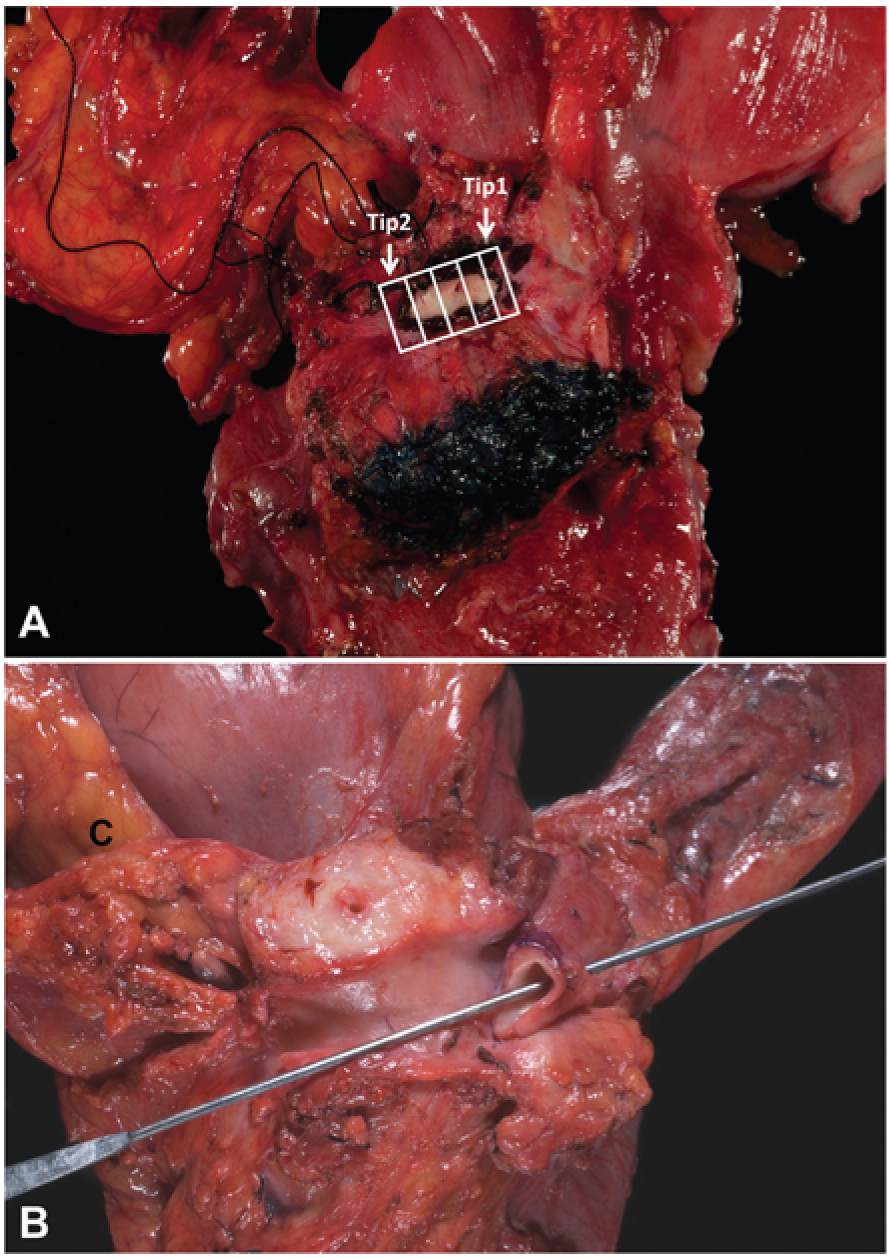

Figure 17-4. A. Pancreaticoduodenectomy specimens with patch resection of superior mesenteric vein (SMV). The SMV margin should be inked and the patch of SMV should be serially sectioned and entirely submitted with the underlying tumor in a fashion similar to a skin ellipse. B. Pancreaticoduodenectomy specimens with segmental resection of SMV.

d. Open small bowel along the serosal side opposite to the pancreatic head and open stomach along the greater curvature.
e. Carefully examine the mucosal surface of small bowel, ampulla of Vater, and stomach for mass lesion, ulcer, polyp, or other abnormalities. The distal portion of the small bowel is usually dusky because the blood supply to this portion is ligated earlier during the operation.
f. While some schools advocate axial sectioning of the pancreas, most, including us, perform the “bivalving” approach in which the head of the pancreas is bivalved at a plane that goes through both main pancreatic ducts (MPD) and CBD. If the latter approach is chosen, the following needs to be performed: Insert a probe in CBD and a probe in MPD to ampulla of Vater. CBD is probable all the way to the ampulla in every patient, however, tracking the MPD to the ampulla may not be achievable in a quarter of the cases due to the narrowness of the duct and the kink in the middle. However, it is typically possible to follow the MPD about a third of the way, which is enough for the bivalving approach to be performed. Bisect the head of pancreas along the two-duct plain or cut the pancreas in a butterfly fashion along the probes to the ampulla of Vater and open the common bile duct, which will give the best demonstration of the tumor epicenter and the relationship of tumor to ampulla of Vater, duodenum, CBD, and pancreas (Figure 17-5A).

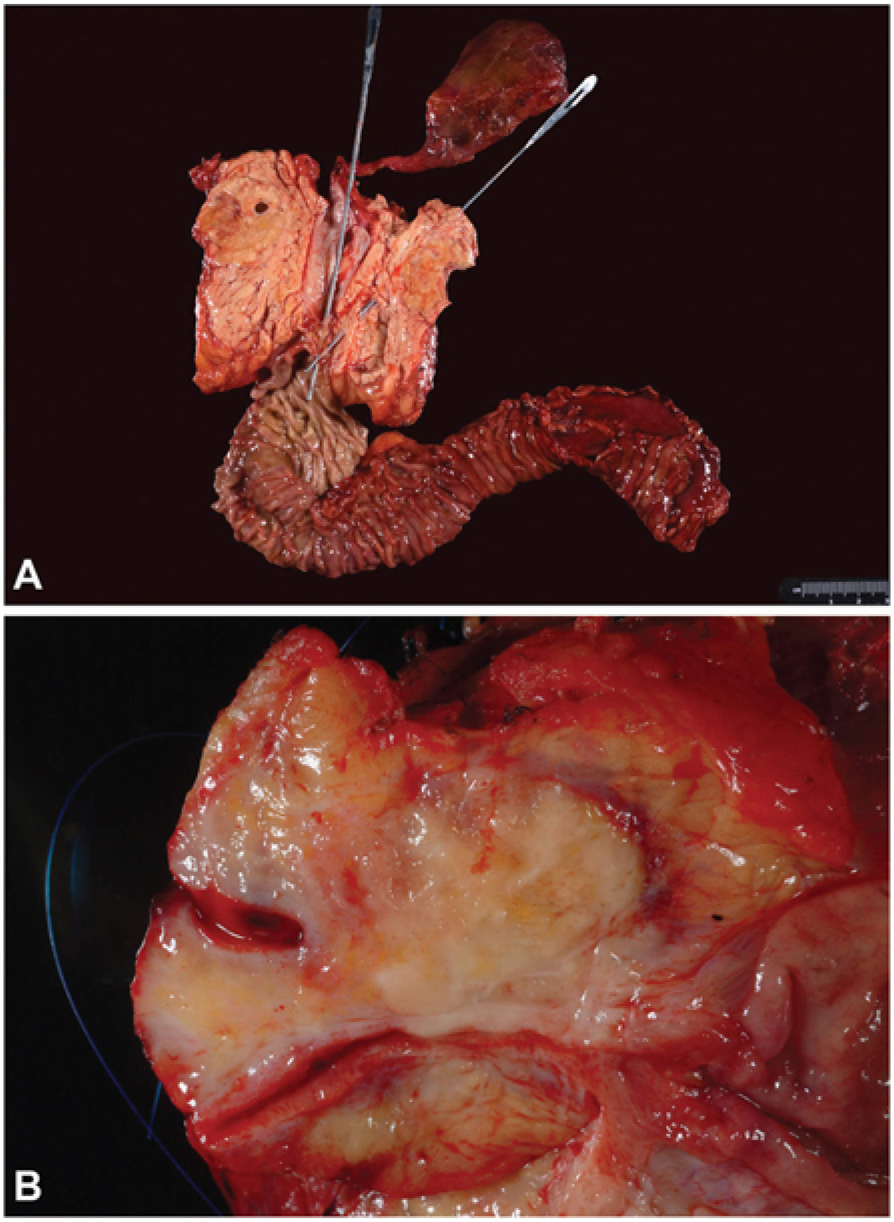

Figure 17-5. A. Head of the pancreas bivalved in a butterfly fashion along the two-duct plain, which goes through both main pancreatic duct and common bile duct (CBD) (marked by two probes) to the ampulla of Vater and opens the common bile duct, demonstrates a mass lesion epicentered in the head of the pancreas and its relationship to ampulla of Vater, duodenum, and CBD. B. Gross photo showing a pancreatic ductal adenocarcinoma forming an ill-defined, infiltrating mass in pancreatic head.

g. Examine CBD, the ampulla of Vater, and pancreas for mass lesion and determine the epicenter of mass lesion in the specimen. This is critical to determine the primary site of the tumor. Pancreatic neoplasm should be centered in the head of the pancreas (Figure 17-5B). The tumor location within the pancreas should also be specified (pancreatic head, uncinate process, pancreatic neck/body, and pancreatic tail) as required in the CAP protocol. It is not uncommon for pancreatic ductal adenocarcinoma or other types of pancreatic neoplasms invading into adjacent CBD, ampulla of Vater, and duodenum. However, this should not be misinterpreted as neoplasm of ampulla of Vater, duodenum, or CBD. Carcinoma of ampulla of Vater should be centered at the ampulla of Vater and involves the entire ampulla of Vater. The carcinoma of CBD typically forms a concentric mass around the bile duct. Primary duodenal carcinoma often forms a duodenal mucosal-based polypoid or ulcerated mass with no or only partial involvement of ampulla of Vater or pancreas. In some studies, no involvement of ampulla itself is used as the criteria for the diagnosis of nonampullary duodenal carcinomas.[13,14]

h. Fixation of the pancreaticoduodenectomy and total pancreatectomy specimens allows better orientation of the sections with soft tissue neighboring. This is especially true for the ampullary tumors where the documentation of the carcinoma invasion to periduodenal soft tissue is crucial.
i. Describe the tumor in gross description: the location of tumor, number of tumor, tumor size, nature (solid vs cystic), circumscription, the cut surfaces (consistency, necrosis, hemorrhage), tumor involvement of MPD and adjacent organs or structures, such as duodenum, ampulla of Vater, CBD, retroperitoneal/peripancreatic soft tissue, SMV/PV, stomach, omentum, or other adjacent organ(s) and the distance from all margins. In addition, tumor involvement of posterior surface of pancreas, anterior surface of pancreas, and vascular bed (SMV/PV groove) should also be documented.
j. For cystic lesions of the pancreas, describe any communication between the lesion and pancreatic ducts, cystic contents (mucin or serous fluid, necrotic tissue, etc), the presence or absence of intracystic mural nodule or mass. For the determination of the size of thin-walled cyst, which may be ruptured during transport/processing, correlation with the radiologic findings is indicated and should be documented accordingly.
k. Describe the secondary gross finding in stomach, duodenum, ampulla of Vater, CBD, pancreas, variations of the merger of the common bile duct and main pancreatic duct, and gallbladder if present.
l. Lymph node dissection is important for the AJCC staging and prognosis. A minimum of 12 lymph nodes is recommended for pancreaticoduodenectomy specimens. More recent studies from major institutions indicate that median number of lymph nodes identified is 17. Most lymph nodes can be identified by careful sectioning and palpating of the peripancreatic and retroperitoneal soft tissue, and adipose tissue attached to the stomach. Based on the current CAP protocol, anatomic division of lymph nodes is not necessary, but separately submitted lymph nodes should be individually reported. The orange-peeling method for lymph node harvest in pancreatoduodenectomy specimens, in which peripancreatic soft tissues are shaved off after submitting pancreatic margin, bile duct margin, and the entire retroperitoneal margin perpendicularly (inked and bread-loafed at 3-mm thick slice), has been reported to increase the yield in number of lymph nodes and optimizes staging for pancreatic ductal adenocarcinoma.[15] This allows the separation of the lymph nodes before the fragmentation of the pancreatic head, at which time finding the lymph nodes embedded in the “peripancreatic soft tissues” becomes more challenging.
m. General recommendation for section submission:
(1) Pancreatic parenchymal margin, CBD margin, and retroperitoneal margins and resected SMV/PV if present as described above.
(2) One representative section each from the proximal gastric margin and distal small bowel margin is often adequate, unless the tumor is a duodenal neoplasm that is close to the margins, or the microscopic examination reveals an unusual malignancy like poorly cohesive tumor cells. These sections also serve as documentative sampling of the gastric/intestinal segments of the specimen, and thus additional representative sections of normal small bowel and stomach are often not necessary.
(3) Representative sections of the tumor, at least one representative section per centimeter of tumor size, and tumor in relationship with duodenum, ampulla of Vater, CBD, or other organs. If it is possible, continuous mapping sections crossing the largest dimension of the tumor should be considered to validate the gross measurement of tumor size.
(4) Representative sections of the secondary pathology identified in the specimen.
(5) One or two representative sections of the uninvolved pancreas and ampulla of Vater.
(6) Sections of all possible lymph nodes.
2. Grossing of the distal pancreatectomy with or without splenectomy
a. Describe all components in the specimen and record the dimensions of the pancreas, spleen, attached adipose tissue, and other organs if present.
b. Identify and submit the pancreatic parenchymal margin for frozen section if requested.
c. For sectioning of the pancreas, most institutions including ours perform bisection of the pancreas along the long axis of pancreas, through the plane of the pancreatic duct; however, this may leave two very thin

slices of pancreas and make it difficult to appreciate the tumor extension to the surfaces (Figure 17-6). Therefore, radial breadloafing of the pancreas becomes a consideration, especially for the pancreata that are very thin. Describe the tumor location, the closest distance from tumor to pancreatic margin, number of tumor, tumor size, nature (solid vs cystic), circumscription, the cut surfaces (consistency, necrosis, hemorrhage), tumor involvement of pancreatic duct and the adjacent organs, such as stomach, spleen, splenic vein or artery, etc. If the tumor invades into a large vessel, the vessel margin should be submitted for histologic examination. Representative sections of the tumor and the pancreas should be submitted as described in pancreaticoduodenectomy specimens.

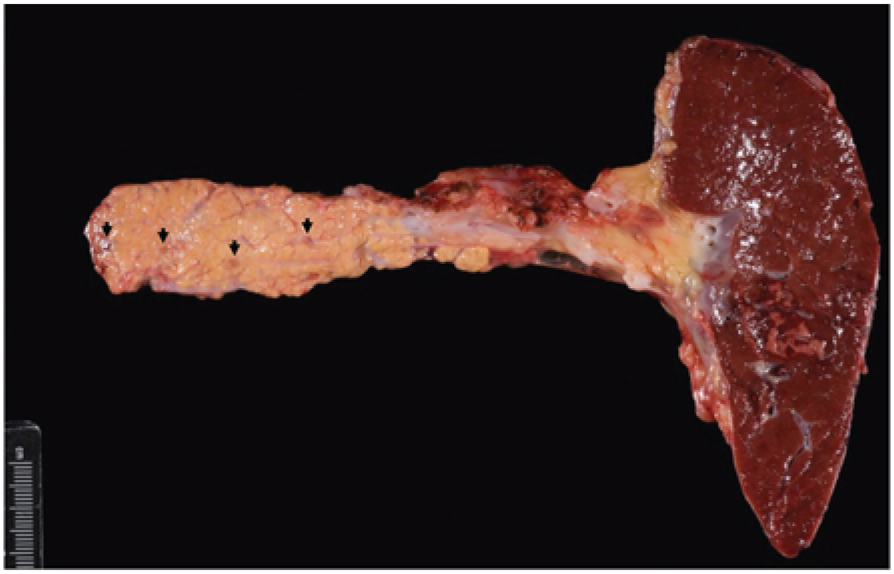

Figure 17-6. A distal pancreatectomy and splenectomy specimen bisected along the long axis of pancreas through the plane of the pancreatic duct showing multiple well-differentiated pancreatic neuroendocrine tumors (arrows) in a patient with multiple endocrine neoplasia type 1 (MEN1) syndrome.

d. Serially section through the spleen to evaluate tumor involvement and to identified other lesions in the spleen. If spleen is grossly unremarkable, one or two representative sections of spleen should be submitted.

e. Lymph nodes are invariably present in peripancreatic soft tissue and the adipose tissue adjacent to the hilum of spleen. Although there is no minimal number of lymph nodes required for distal pancreatectomy specimens, careful dissection of all possible lymph nodes is important for accurate lymph node staging.

3. Grossing partial/segmental pancreas resection specimen

a. Record the dimension of the pancreas, ink both pancreatic margins in different colors.

b. For cystic lesions, insert a probe in the pancreatic duct from one pancreatic margin to the other pancreatic margin, bisect the pancreatic along the probe, document whether the cystic lesion involves the pancreatic duct (Figure 17-7).

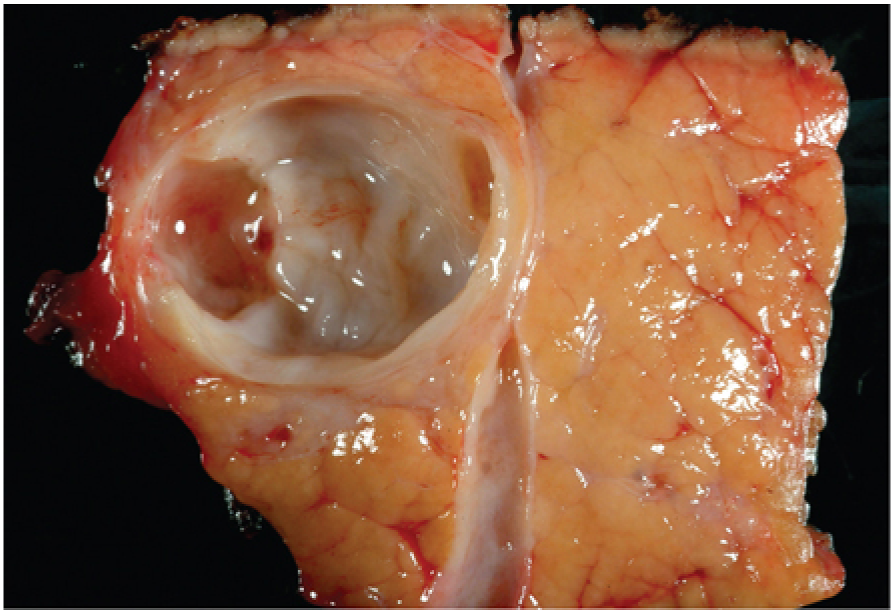

Figure 17-7. A segmental resection specimen of the pancreas bisected along the plain of pancreatic duct showing small mucinous cystic neoplasm that has no communication with the pancreatic duct.

c. Serially section the specimen, describe the closest distance from tumor or cyst to pancreatic margins, tumor size, nature (solid vs cystic), circumscription, the cut surfaces (consistency, necrosis, hemorrhage). The entire tumor with adjacent pancreas may be submitted.

d. Two pancreatic margins can be submitted either en face or perpendicular to the tumor for frozen sections or permanent sections depending on the distance from the tumor to pancreatic margins.

4. Grossing of the enucleation specimen of pancreatic neoplasm

a. Record the dimensions of the specimen.

b. Ink the specimen surface and block excess ink.

c. Serially section the specimen, describe tumor size, nature (solid vs cystic), the cut surfaces (consistency, necrosis, hemorrhage), and submit the entire specimen.

VI. Special considerations

1. For mucinous cystic lesions of the pancreas, such as mucinous cystic neoplasm or intraductal papillary mucinous neoplasm etc, the tumor should be carefully examined for any mural nodule or mass of invasive carcinoma. In addition, gross involvement of the pancreatic duct should be documented in the gross description. If no invasive carcinoma is identified grossly or on representative sections, the entire cystic lesion may have to be submitted for histologic examination to rule out invasive carcinoma. This is critical for the postsurgical management of the patient and the prognosis.

2. For specimens (treated or untreated), in which no gross lesion is identified after careful gross examination, it is recommended that the entire pancreas, CBD, and ampulla of Vater should be submitted for histologic examination.

VII. Example of gross description of a pancreaticoduodenectomy specimen using the paragraph system

HEAD OF PANCREAS, DISTAL STOMACH, DUODENUM, DISTAL COMMON BILE DUCT – A pancreaticoduodenectomy that is consisted of the head of pancreas (7.5 x 5.5 x 4.0 cm), a segment of common bile duct with a metallic stent (6.0 cm in length x 0.7 cm in diameter), a portion of distal stomach (8.0 x 4.2 x 2.5 cm) and segment of duodenum and jejunum (17.5 cm in length x 5.5 cm in circumference).

There is a solid, infiltrative mass, 4.2 x 3.1 x 2.6 cm that is located in the head of pancreas. The cut surface of the tumor is tan-white, firm, and fibrotic with no obvious necrosis or hemorrhage. Grossly the tumor involves main pancreatic duct and invades into duodenal wall forming a puckered area on the duodenal mucosa

measuring 0.6 cm in greatest dimension. The tumor grossly does not involve ampulla of Vater, common bile duct, or stomach. The tumor is grossly 1.5 cm from retroperitoneal margin, 1.0 cm from the common bile duct margin, 1.0 cm from the pancreatic parenchymal margin, 10.0 cm from the proximal margin, and 14 cm from the distal margin.

The metallic stent (5.0 cm in length x 0.6 cm in diameter) is partially protruding from the ampulla of Vater. The adjacent mucosa in the periampullary region shows ulceration/erosion (1.5 cm in largest dimension). The uninvolved pancreas shows moderate fibrosis consistent with chronic pancreatitis. Distal stomach and the rest of duodenum and jejunum are grossly unremarkable. The common bile duct wall is fibrotic secondary to the metallic stent and otherwise unremarkable. Multiple possible lymph nodes are identified in the peripancreatic adipose tissue ranging in size from 0.3 cm to 1.2 cm in greatest dimension. A portion of tumor and uninvolved pancreatic tissue and duodenal mucosa are submitted for tumor bank. The specimen is representatively submitted.

Ink code: Black – retroperitoneal margin.

Section code

A1-A2: Entire pancreatic parenchymal (neck) margin, en face, for frozen section diagnosis and permanent section

A3: Common bile duct margin, en face, for frozen section diagnosis and permanent section

A4-A10: Retroperitoneal resection margin, perpendicular, entirely submitted

A11: Representative section of proximal gastric margin

A12: Representative of distal small bowel margin

A12-A14: Ampulla of Vater, radially sectioned, entirely submitted

A15-A16: The puckered area of duodenal mucosa with underlying tumor

A17-A18: Representative section of the tumor adjacent to common bile duct

A19-A24: Sequential sections across the largest diameter of the tumor with adjacent normal tissue in A19 and A24 for tumor size validation, the matching tissue edges between the blocks are inked blue

A25: Representative sections of the uninvolved pancreas

A26: The ulcer in the periampullary region, entirely submitted

A27-A32: Each containing four possible lymph nodes

A33: Three possible lymph nodes

A34: One possible lymph node serially sectioned

VIII. Synoptic pathology reporting

The current CAP protocol requires the following parameters to be included in the final pathology report:

- Specimen: List all organs/components, including SMV or PV if present in the specimen.
- Procedure: Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy vs total pancreatectomy; partial pancreatectomy, pancreatic body vs pancreatic tail; or other.
- Tumor site: Pancreatic head, uncinate process, pancreatic body, pancreatic tail, or other.
- Tumor size: Greatest dimension in cm and additional dimensions: ___ x ___ cm.
- Histologic type using the WHO Classification of Tumors of the Pancreas.
- Histologic grade: For carcinoma of the pancreas (G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; and G4: undifferentiated) and for well differentiated pancreatic neuroendocrine tumors (G1, G2, and G3 based on the mitotic rate and Ki-67 labeling index).
- For pancreatic well-differentiated neuroendocrine tumors, the tumor focality (unifocal, multifocal [specify number of tumor], or cannot determined), functional type if applicable, mitotic rate (number of mitoses in 2 mm^2), Ki-67 labeling index, and tumor necrosis should also be reported.
- Microscopic tumor extension.
- Margins and the distance of invasive carcinoma from closest margin in mm or cm if all margins uninvolved by invasive carcinoma.
- Treatment effect if patient received neoadjuvant therapies:

- No viable cancer cells (complete response, score 0)
- Single cells or rare small groups of cancer cells (near complete response, score 1)
- Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
- Extensive residual cancer with no evident tumor regression (poor or no response, score 3)

• Lymph-vascular invasion: Not identified or present. If present, specify small vessel lymph-vascular invasion or large vessel (venous) invasion.
• Perineural invasion: Not identified or present.
• Pathologic staging (pTNM): Microscopic evaluation of at least 12 lymph nodes is recommended for Whipple resections.
• Additional pathologic findings.
• Clinical history.

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18. Perihilar Bile Ducts

Wai Chin Foo, MD

Extrahepatic bile duct tumors include both proximal (or perihilar) and distal bile duct tumors. Perihilar cholangiocarcinomas are defined as tumors that involve the main lobar extrahepatic bile ducts distal to the segmental bile ducts and proximal to the confluence of the cystic duct and common hepatic duct; they represent 50% to 70% of all cases of bile duct carcinomas. In the United States, the incidence of perihilar cholangiocarcinomas is 1 to 2 per 100,000 cases.[1] As with other biliary tract malignancies, the most common risk factors are primary sclerosing cholangitis, ulcerative colitis, anomalous choledochopancreatic junctions, and certain infections.[2]

This chapter focuses on the appropriate handling of perihilar resections. Given that complete resection with microscopic negative margins is the most robust predictor of long-term survival, the identification of the appropriate margins is critical and will be discussed along with gross examination, adequate sampling, and reporting of resection specimens using the College of American Pathologists (CAP) cancer protocol.

The pathologist plays an important role in guiding subsequent therapeutic approaches after resection. As such, proper handling of the gross specimen, accurate histologic evaluation, and concise and meaningful reporting is critical.

I. Indications for resections

In general, patients with cholangiocarcinoma are commonly diagnosed when the disease is advanced; subsequently, prognosis is dismal. However, complete resection has been associated with long-term survival,[3] and it remains the best option for patients with cholangiocarcinoma. Surgical resections include total hepatectomies and extended hepatectomies with or without caudate lobectomies. Segmental resection of localized disease has largely been abandoned in favor of more aggressive approaches. In general, the criteria for resectability in the United States include absence of retropancreatic and paraceliac nodal disease, absence of invasion of the main portal vein or main hepatic artery, absence of extrahepatic organ invasion, and absence of disseminated disease.[4]

II. What to expect grossly and microscopically

A review of the clinical and radiologic findings can be useful before the gross evaluation (see Figure 18-1). Variations of the arterial, venous, and biliary anatomy are not uncommon.[5,6] In addition, the Bismuth-Corlette classification of the tumor may be provided; this classification system provides a description of the anatomic location of the tumor as well as its longitudinal extension in the biliary tree[7] (see Table 18-1). Understanding the relationship of the tumor to the vasculature and the biliary tree before sectioning is important. In the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, T3 is defined as unilateral involvement of the branches of the portal vein or the hepatic artery, and T4 is defined as involvement of the main portal vein or its branches bilaterally, the common hepatic artery, or the second-order biliary radicals unilaterally with contralateral portal vein or hepatic artery involvement.[8,9] In most instances, T3 and T4 tumors will be determined by imaging.[9]

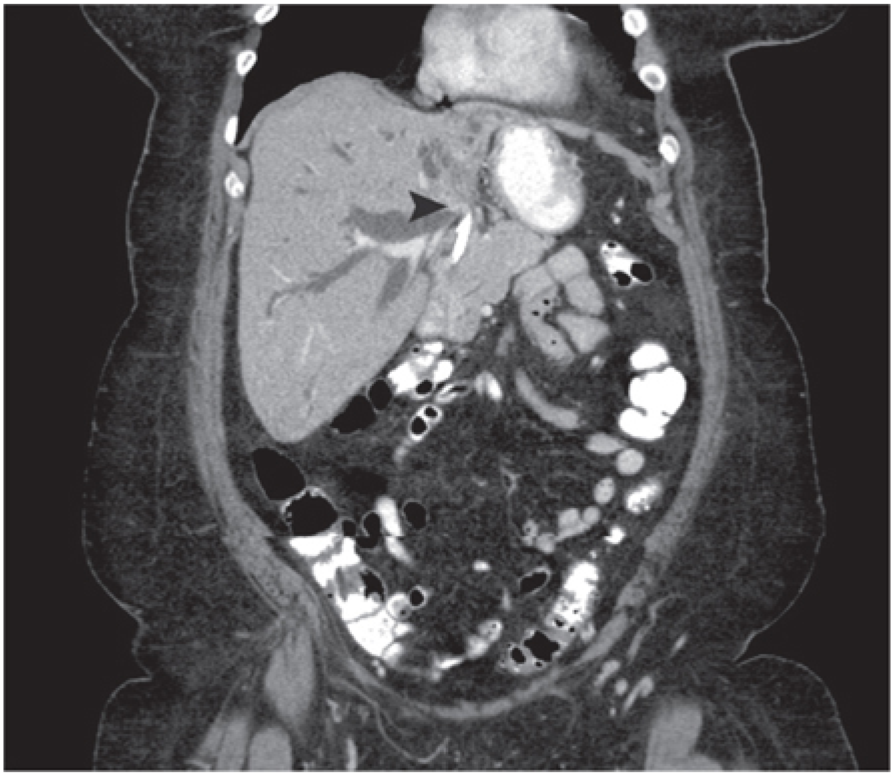

Figure 18-1. Abdominal computed tomography. There is a tumor occupying the hilum (arrowhead). There is proximal duct dilation in both lobes of the liver, but it is more pronounced in the left lobe. In addition, the left lobe of the liver is atrophied.

Table 18-1. Bismuth-Corlette Classification

Type	Definition
I	Tumor is limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts.
II	Tumor involves the confluence of the right and left hepatic ducts.
IIIa	Tumor involves the confluence of the right and left hepatic ducts AND extends to the right second-order ducts.
IIIb	Tumor involves the confluence of the right and left hepatic ducts AND extends to the left second-order ducts.
IV	Tumor involves the confluence of the right and left hepatic ducts AND extends to both the right and left second-order ducts.

Bile duct carcinomas are thought to develop from either a mass-forming precursor (eg, intraductal papillary neoplasm of the bile duct [IPNB]) or a non–mass-forming (flat) precursor (eg, biliary intraepithelial neoplasia [BilIN]). The former can be identified grossly intraductally. IPNBs encompass tumors that were previously called papillomas, papillary adenomas, and papillary adenocarcinomas. Microscopically, IPNBs can resemble intraductal papillary mucinous neoplasms (IPMNs) of the pancreas and are similarly characterized by atypical epithelial cells with pancreaticobiliary-type, intestinal-type, and gastric-type morphology. IPNBs can be further divided into low, intermediate, and high grades on the basis of the degree of dysplasia. BilINs are characterized by atypical epithelial cells with multilayering of the nuclei and micropapillary architecture. BilINs are divided into BilIN-1 (low grade), BilIN-2 (intermediate grade), and BilIN-3 (high grade) on the basis of the degree of

dysplasia. These lesions can also involve the peribiliary glands and can be misinterpreted as invasion. BilINs in the extrahepatic bile ducts resemble those found in the intrahepatic biliary tree.[2]

III. Typical gross photographs of resections

Perihilar resections can be difficult to orient due to the number of important "tubular" anatomic structures (eg, portal vein and/or branches of; hepatic artery and/or branches of; and bile duct) in a small location. In addition, variant anatomy for both the vasculature and biliary system is common. An awareness of the Bismuth-Corlette classification for the tumor can help guide the dissection (see Figures 18-2 and 18-3).

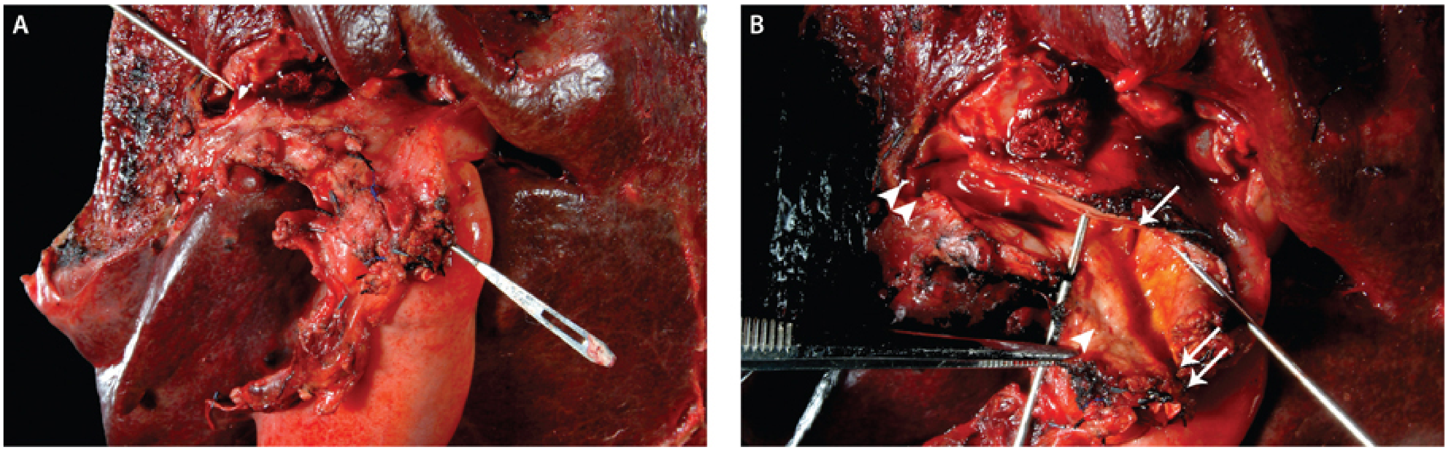

Figure 18-2. Extended right hepatectomy specimen. A. The probe enters the common hepatic duct and exits the left hepatic duct. B. The type II tumor (arrowhead) is located in the common bile duct and extends to the confluence of the right and left hepatic ducts. The right hepatic duct (arrow) dives into the liver, and the left hepatic duct (double arrowhead) and the common hepatic duct (double arrow) are both transected (proximal and distal bile duct margins, respectively).

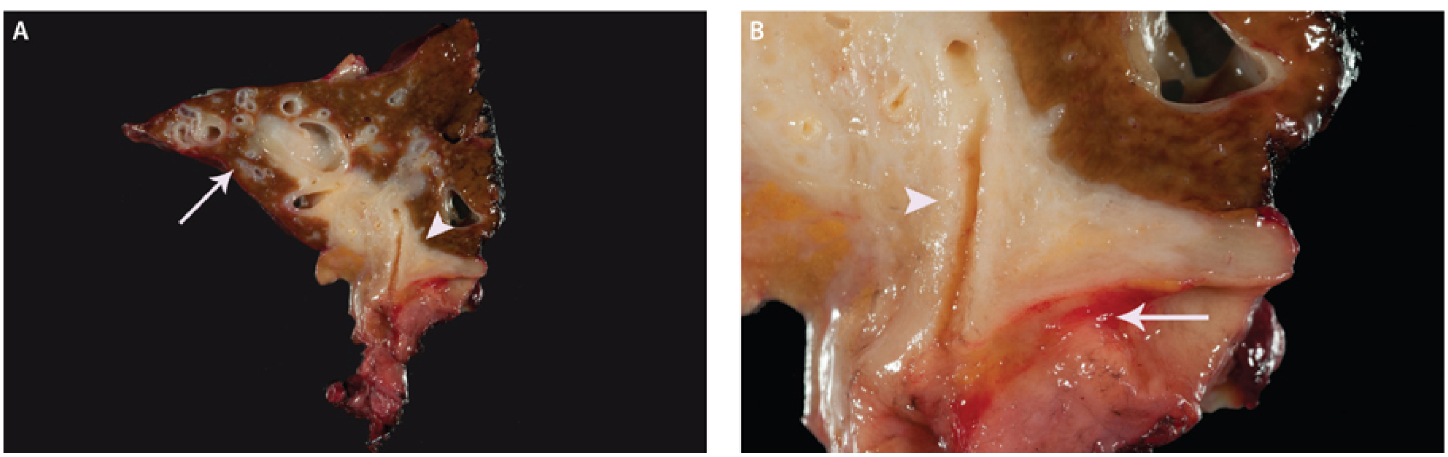

Figure 18-3. Extended left hepatectomy specimen. A. The type IIIb tumor (arrowhead) is located in the left hepatic duct and is associated with proximal duct dilation (arrow) and atrophy of the left lobe of the liver. B. The tumor involves the confluence of the right hepatic duct (arrow) and the left hepatic duct (arrowhead).

IV. Dissection techniques

Hilar and hepatic resection

1. Orient the specimen and assess the overall appearance of the liver.

a. Identify the bile ducts (eg, common hepatic duct, right hepatic duct) and, if applicable, the main portal vein (or its branches) and the hepatic artery (or its branches). Sutures placed by the surgeon may indicate the structures.

2. If frozen section evaluation of the duct margins is requested, submit the margins en face.

3. Section the specimen thinly.

a. The bile ducts can be opened longitudinally. If a palpable tumor is present, try to avoid cutting across the tumor. This method allows for visualization of the tumor and its relationship with the other structures.

b. The bile duct can be serially sectioned. Differential inking of the lumen can be used to identify the bile ducts microscopically.

4. Record the size of the tumor, and describe the characteristics of the tumor (eg, mass-forming, intraductal, flat) and the location of the tumor (confirming the Bismuth-Corlette classification).

5. Collect fresh tissue for tissue banks (if applicable) following institutional and protocol guidelines.

a. A frozen section of the harvested tissue can be performed, if requested, in order to confirm the presence of tumor.

6. Lay the slices of the specimen flat and fix the specimen overnight.

7. If the bile duct or vascular margins were not previously evaluated intraoperatively, submit the margins en face.

8. Section the tumor perpendicular to the longitudinal axis. Describe the depth of invasion. Take sections to demonstrate the tumor to nearby vasculature.

9. Describe the remainder of the liver (eg, presence of duct dilation, atrophy).

Total hepatectomy

1. Orient the specimen and assess the overall appearance of the liver.

a. Identify the bile ducts (eg, common hepatic duct, right hepatic duct) and, if applicable, the main portal vein (or its branches) and the hepatic artery (or its branches). Sutures placed by the surgeon may indicate the structures.

2. If frozen section evaluation of the duct or vascular margins is requested, submit the margins en face.

3. Section the specimen thinly.

a. The bile ducts can be opened longitudinally. If a palpable tumor is present, try to avoid cutting across the tumor. This method allows for visualization of the tumor and its relationship with the other structures.

b. The bile duct can be serially sectioned. Differential inking of the lumen can be used to identify the bile ducts microscopically.

4. Record the size of the tumor, and describe the characteristics of the tumor (eg, mass-forming, intraductal, flat) and the location of the tumor (confirming the Bismuth-Corlette classification).

5. Collect fresh tissue for tissue banks (if applicable) following institutional and protocol guidelines.

a. A frozen section of the harvested tissue can be performed, if requested, in order to confirm the presence of tumor.

6. Lay the slices of the specimen flat and fix the specimen overnight.

7. If the bile duct or vascular margins were not previously evaluated intraoperatively, submit the margins en face.

8. Section the tumor perpendicular to the longitudinal axis. Describe the depth of invasion. Take sections to demonstrate the tumor to nearby vasculature.

9. Describe the remainder of the liver (eg, presence of duct dilation, atrophy), and take sections of both lobes of the liver.

V. Gross descriptions

The gross description provides context for the microscopic findings. As such, it is important to describe whether or not an intraductal, mass-forming tumor is present. Invasive carcinomas that arise in IPNBs are associated with a higher median disease-specific survival after resection.[10] In addition, the location of the tumor and the relationship to the biliary tree and the portal vein and hepatic artery, if applicable, should be included. By providing this information, the radiologic findings, such as the Bismuth-Corlette classification, can be confirmed, and the tumor can be accurately staged.

Hilar and hepatic resection

Left lobe of liver resection: An extended left hepatectomy specimen consisting of an atrophied left lobe of liver (12 x 7 x 5 cm) with the right hepatic duct (0.2 cm in length x 0.4 cm in diameter), the left hepatic duct

(0.4 cm in length x 0.1 cm in diameter), the common hepatic duct (1 cm in length x 0.5 cm in diameter), and a portion of the left portal vein (0.2 x 0.2 x 0.1 cm). The specimen is oriented with sutures (per surgeon, short stitch = right hepatic duct; long stitch = common hepatic duct; double stitch = portion of left portal vein).

There is an ill-defined, firm, tan/white tumor (3 x 2 x 2 cm) in the hilar soft tissue. The tumor obliterates the common hepatic duct and involves the confluence of the left and right hepatic ducts. The portion of the left portal vein is adherent to the tumor, but no definite invasion into the wall of the vein is present. The tumor invades the liver. The tumor is 1.5 cm from the proximal right hepatic duct margin, 2.1 cm from the distal common hepatic duct margin, 0.1 cm from the left portal vein margin, 0.1 cm from the hilar soft tissue (radial) margin, and 0.1 cm from the parenchymal margin. The bile duct in the left lobe proximal to the tumor is dilated, and the left lobe is atrophied.

Ink code

Parenchymal margin - black

Serosa - blue

Hilar soft tissue (radial) margin - orange

Section code

FSA1: Proximal right hepatic duct margin, en face

FSA2: Distal common hepatic duct margin, en face

A3: Tumor and closest parenchymal margin

A4: Tumor and closest hilar soft tissue (radial) margin

A5-A6: Tumor and left portal vein, in toto

A7-A8: Tumor and confluence of left and right hepatic ducts, representative

A9: Tumor and liver, representative

A10: Uninvolved liver with dilated bile ducts, representative

Total hepatectomy

Liver: A total hepatectomy specimen that includes the liver (1200 g; 21 x 18 x 8 cm), the gallbladder (8 cm in length x 1-4 cm in circumference; 0.3 cm in wall thickness), common duct (2 cm in length x 0.5 cm in diameter), the portal vein (2 cm in length x 1 cm in diameter), and the hepatic arteries (1.8 cm in length x 0.5 cm in diameter). The hepatic arteries, portal vein, and common bile duct are oriented by sutures (per surgeon, single stitch = hepatic artery; double stitch = portal vein; long stitch = common bile duct).

There is an ill-defined, firm tan/white tumor (3 x 2 x 2 cm) in the hilum. The tumor obstructs the common hepatic duct, involves the confluence of the left and right hepatic ducts, and extends to the right second-order biliary radicals (right anterior and right posterior ducts). The portal vein and hepatic arteries are not involved. The tumor abuts the liver, but no unequivocal invasion into the parenchymal is identified. The tumor is 1.8 cm from the common duct margin, 0.5 cm from the hilar soft tissue (radial) margin, 1.8 cm from the portal vein margin, and 1.8 cm from the hepatic arterial margins.

There is bile duct dilation in the left and right lobes of the liver.

Ink code

Serosa - blue

Hilar soft tissue (radial) margin - orange

Section code

FSA1: Common duct margin, en face

FSA2: Portal vein margin, en face

FSA3: Hepatic arterial margins, en face

A4: Tumor and closest hilar soft tissue (radial) margin

A5-A6: Tumor in the common hepatic duct, representative

A6-A7: Tumor and confluence of left and right hepatic ducts, representative

A8: Tumor involvement of the right anterior and right posterior duct confluence, representative

A9: Tumor and liver, representative

A10: Uninvolved left lobe liver with dilated bile ducts, representative

A11: Uninvolved right lobe liver with dilated bile ducts

VI. Common pathologic findings

Adenocarcinoma (or perihilar cholangiocarcinoma) is the most common malignancy seen in these specimens (see Figure 18-4). The adenocarcinoma may be associated with a mass-forming precursor (eg, IPNB or BilIN) (see Figure 18-5). However, a precursor is not always identified. Adenosquamous carcinoma and squamous cell carcinoma can also be seen and resemble their counterparts in the distal extrahepatic bile ducts and gallbladder (see Figure 18-6). In addition, because these tumors frequently obstruct the biliary tree, proximal bile duct dilation and atrophy of the liver can be seen (see Figure 18-3).

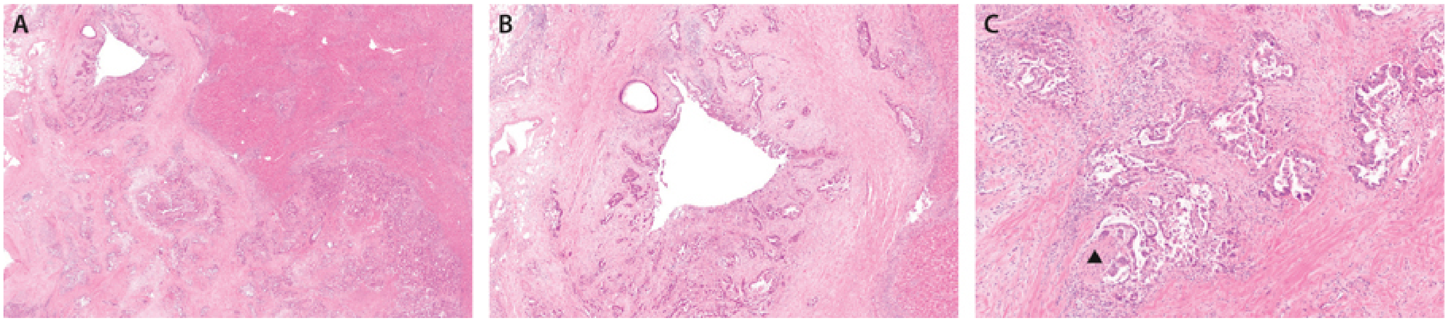

Figure 18-4. Adenocarcinoma. A. Adenocarcinoma occupies the hilum with circumferential involvement of a bile duct (left) and invasion into the liver (right). B. A higher-power view of the involved bile duct shows no intraductal growth; however, flat dysplastic epithelium is present. C. In this field, the adenocarcinoma shows biliary-type morphology, but subtyping is not required in the College of American Pathologists cancer protocol.[9] A focus of perineural invasion is present.

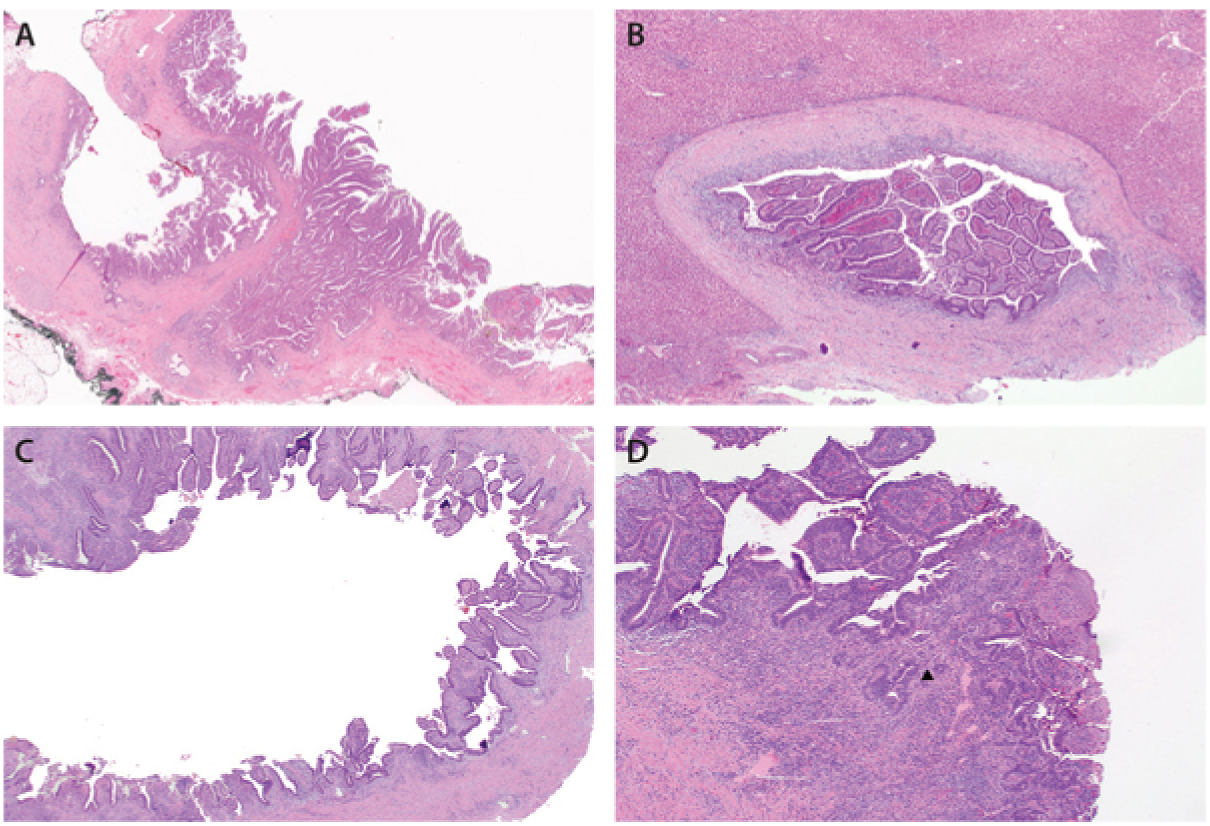

Figure 18-5. Precursor lesions. A. Intraductal papillary neoplasm of the bile duct (IPNB) involving the confluence of the right hepatic duct (inked yellow, right side) and the left hepatic duct (inked red, left side). B. IPNB with intermediate-grade dysplasia extending into a segmental bile duct. C. The common hepatic duct mucosa is abnormal, with an undulating architecture and focal papillae (right side). D. In this field, biliary intraepithelial neoplasia-3 (high grade) with a focus of invasive carcinoma (arrowhead) is present.

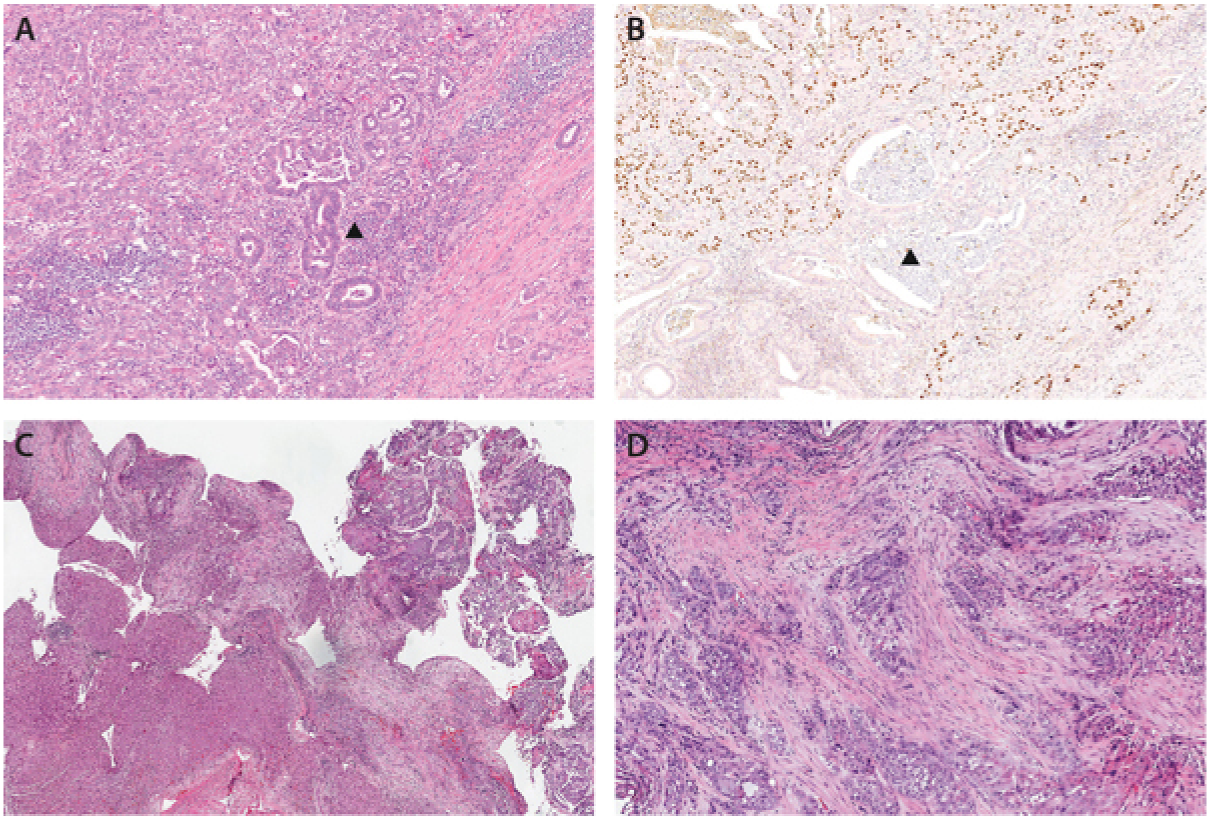

Figure 18-6. Other histologic types. (A) Adenosquamous carcinoma with (B) p40 positivity in the squamous component but not in the glandular component (arrowhead) (C, D) Squamous cell carcinoma.

VII. Common potential pitfalls and solutions

Pathologic staging of hilar cholangiocarcinoma can be difficult owing to the complex, intimate, and variable anatomic relationships of the bile duct and vascular structures. In addition, microscopic demonstration of second-order biliary radical involvement, which is needed for T4 staging, can be difficult without a careful gross evaluation, including differential inking of the resected ducts.[8,9] The CAP recognizes this difficulty, noting that T4 staging is largely based on imaging.[9] Intraductal tumors completely occluding the bile duct can also mimic the appearance of a solid, invasive carcinoma. A careful gross evaluation and recognition of the circumscribed appearance can aid in this distinction. In addition, identifying bile duct epithelium surrounding the "invasive carcinoma" is also helpful.

VIII. What to include in the report?

At minimum, the report should contain the required elements in the CAP cancer protocol.[9] However, the report should also convey critical information that may not be included, as well as provide additional clarification for problematic or complex diagnoses. Often, the "top-line diagnosis" is used to elaborate on the summarized findings in the Synoptic Report. In addition, the Synoptic Report is, by definition, a summary of the entire case.

An example utilizing both the top-line diagnosis and the CAP cancer protocol for a hilar and hepatic resection of a type II perihilar cholangiocarcinoma with radiologic involvement of the left portal vein branch follows.

Final diagnosis

(A) Liver, left lobe, extended left hepatectomy:

Moderately differentiated adenocarcinoma (3 cm in greatest dimension) involving the common hepatic duct and junction of the right and left hepatic ducts (See Synoptic Report/CAP Protocol.)

High-grade intraepithelial neoplasia present at right hepatic duct and common bile duct margins; all margins are negative for invasive carcinoma.

Synoptic report

Procedure: Hilar and hepatic resection
Tumor Site: Junction of right and left hepatic ducts, common hepatic duct
Tumor Size: Greatest dimension – 3 cm
Histologic Type: Adenocarcinoma, biliary type (extrahepatic cholangiocarcinoma)
Histologic Grade: G2: Moderately differentiated
Microscopic Tumor Extension: Tumor invades beyond the wall of the bile duct into surrounding connective tissue; tumor invades adjacent liver parenchyma; tumor invades unilateral branches of the portal vein (left).
Margins:
Hepatic Parenchymal Margin: Uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin: 0.1 cm
Bile Duct Margins: Involved by high-grade intraepithelial neoplasia; uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin: 1.5 cm
Radial Margin: Uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin: 0.1 cm
Lymphovascular Invasion: Present
Perineural Invasion: Present
Regional Lymph Nodes:
Number of Lymph Nodes Involved: 1
Number of Lymph Nodes Examined: 2
Pathologic Staging (pTNM):
TNM Descriptors: Not applicable
Primary Tumor (pT): pT3
Regional Lymph Nodes (pN): pN1
Distant Metastasis: Not applicable
Additional Pathologic Findings: Dysplasia

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19. Small Bowel

Huamin Wang, MD, PhD; Rashmi Samdani, MD

Primary neoplasms of the small bowel are rare, accounting for only 2% of all malignancies of the gastrointestinal tract. The common histologic types of primary neoplasm of small bowl include adenocarcinoma and other types of carcinoma (24-44%), neuroendocrine neoplasm (20-42%), gastrointestinal stromal tumor (7-9%) and lymphoma (12-27%).[1] Given the rarity of primary neoplasms of small bowel, resection of small bowel for primary tumors is uncommon. Resection of small bowel is more often performed for conditions, such as inflammatory bowel disease (eg, Crohn's disease), ischemia, small bowel obstruction, or metastatic tumors, etc.

The majority adenocarcinomas of small intestine arise in periampullary region of duodenum (64%), jejunum (20%), and terminal ileum (15%).[2] Conditions that predispose to small bowel malignancy include familial adenomatous polyposis (FAP),[3] Peutz-Jeghers syndrome,[4] hereditary nonpolyposis colorectal cancer (HNPCC),[5] Crohn's disease,[3,6] and celiac disease.[7] Tumors arising in the setting of Crohn's disease are more often located in terminal ileum and jejunum secondary to longstanding ileal inflammation and grossly resemble sporadic intestinal adenocarcinoma.[6] Neuroendocrine neoplasms, including well-differentiated neuroendocrine tumor and neuroendocrine carcinoma, account for 30% of all neuroendocrine neoplasms of gastrointestinal tract, with middle to distal ileum being the most common site, followed by jejunum and proximal ileum.[1] Duodenal neuroendocrine neoplasm is rare and accounts for only 5.7% to 7.9% of all neuroendocrine neoplasms of gastrointestinal tract.[8] Depending on the tumor location in the small bowel, types of small bowel resections include pancreaticoduodenectomy (Whipple resection, Figure 19-1), segmental resection (Figure 19-2), and ileocolic resection. For superficial and/or small nonampullary duodenal neoplasms, pancreas-preserving segmental duodenectomy, local full-thickness patch resection, and transduodenal submucosal dissection are occasionally performed. This chapter focuses on appropriate gross examination, sampling, pathologic staging, and synoptic reporting of resection specimens for primary neoplasms of small bowel using the College of American Pathologists (CAP) cancer protocol.

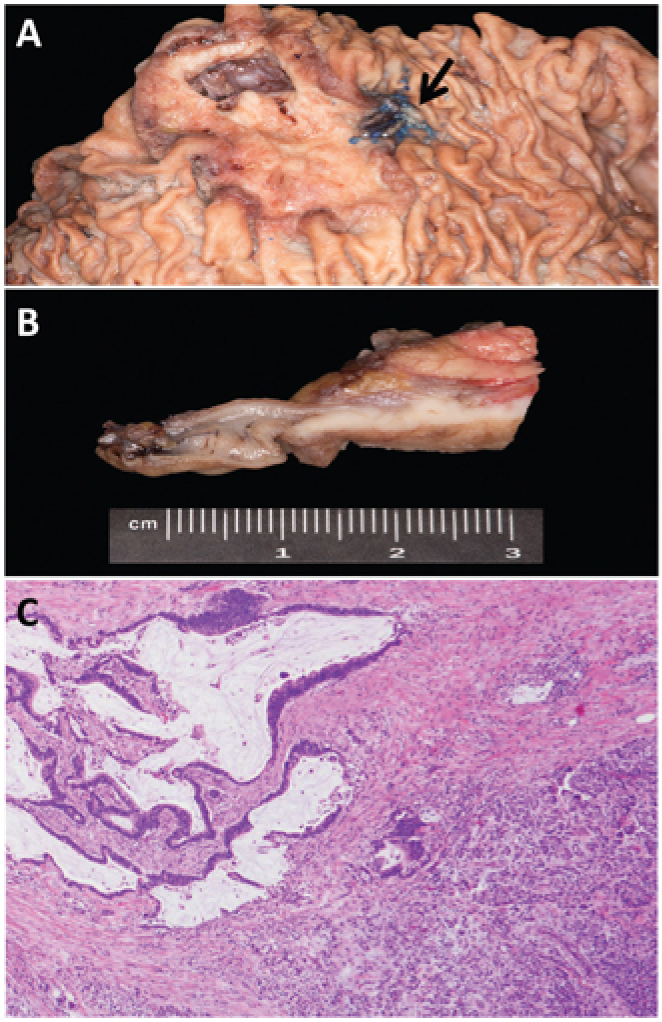

Figure 19-1. A. Pancreaticoduodenectomy specimen showing a duodenal adenocarcinoma forming a mass in periampullary region, but does not involve the ampulla of Vater (arrow head). B. Cross-section of the tumor showing tumor invasion into the periduodenal soft tissue. C. Microscopically, the tumor shows superficial invasion into the head of the pancreas (magnification: 40x).

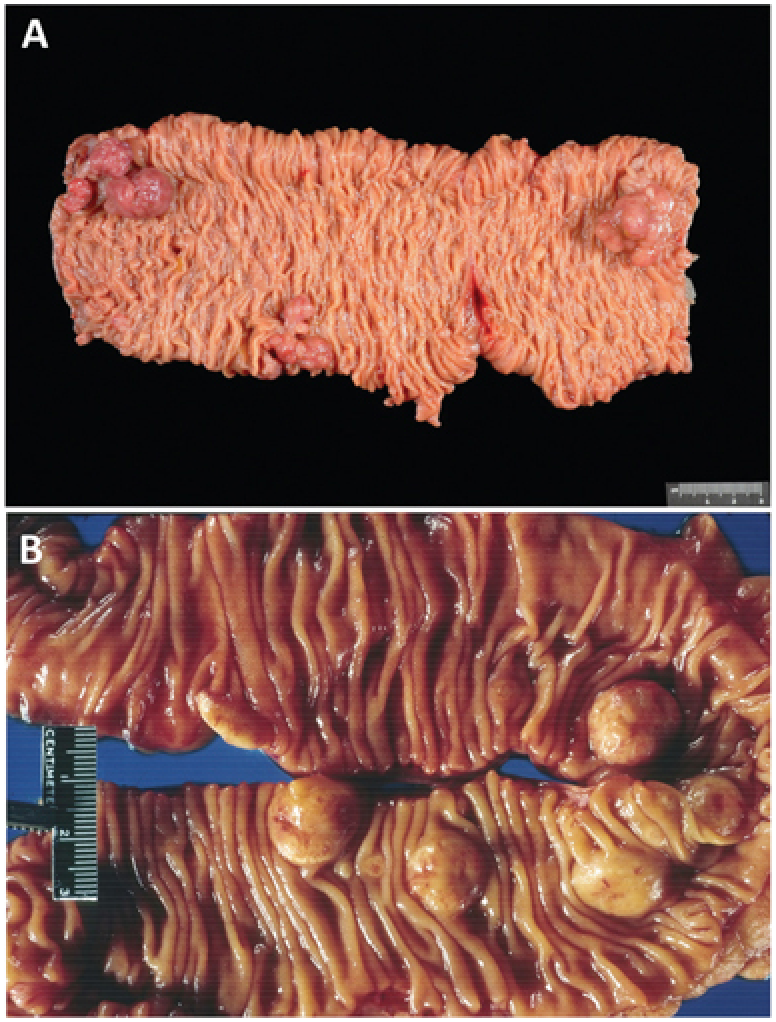

Figure 19-2. A. Segmental resection of small bowel showing three adenomatous polyps in a patient with familial adenomatous polyposis (FAP). B. Segmental resection of small bowel showing multiple well differentiated neuroendocrine tumors.

I. Segmental resection of small bowel and ileocolic resection for small bowel neoplasms

Segmental resection of small bowel and ileocolic resection may be performed for primary neoplasms of small bowel or other conditions, such as inflammatory bowel disease (eg, Crohn's disease), ischemia, bowel obstruction, adenocarcinoma in the cecum and right colon, appendiceal neoplasms, or metastatic tumors, etc. It is important to check the relevant clinical history, endoscopic findings, clinical or biopsy diagnosis if available before grossing these specimens. This is important for proper handling of the specimens as well as histopathologic evaluation, diagnosis, and reporting.

1. Describe all components in the specimen and measure the size of each component. The size of the resected intestine should be measured in length and circumference at the proximal and/and distal resection margins. Depending on the type of tumor in the small bowel, the resected segment of small bowel or ileocolic resection specimen may have variable amount of mesenteric adipose tissue.

2. Check the specimen orientation and identify the proximal, distal, and mesenteric margins. If no orientation is provided, the proximal and distal margin can be arbitrarily designated as margin #1 and margin #2. For all segmental resection specimens of small bowel, except duodenum which has no mesentery and is covered by peritoneum anteriorly, the mesenteric resection margin is the only pertinent radial margin and should be inked with a different color from the ink color used for serosal surface.

For cases in which other organs, such as segment of colon, separate segment of small bowel, retroperitoneal soft tissue, etc, were resected with the small bowel, the margins on these adhered organ(s) should also be properly identified and submitted for histologic examination.

3. Carefully examine the serosal surface for any serosal mass lesion, serosal involvement by the tumor, perforation, or involvement of other organs, ink the serosal surface that is overlying the tumor, and document the number and sizes of serosal tumors and their relationship with other organs if present. The primary neoplasms of small bowel are typically mucosal-based lesions with an outward invasive growth pattern grossly. When multiple serosal tumors are present or the tumor is a serosal-based lesion with inward invasive growth into the wall and/or mucosa of small bowel, the tumor more likely represents a metastasis.

4. Localize the tumor by palpating the specimen, open the small bowel at the antimesenteric side from one end to the other while probing the lumen with your finger to avoid cutting through the tumor. For well-differentiated neuroendocrine tumor (carcinoid tumor), the primary tumor may be very small, careful inspection and palpation of the small bowel mucosa may be needed to find the primary tumor.

5. Describe the number, gross configuration (endophytic ulcerated mass, polypoid mass, diffusely infiltrative or annular mass, etc), and location of the tumor. Measure the tumor size in three dimensions and document the distances of the tumor to all margins in centimeters, including the distance to mesenteric margin and proximal and distal resection margins. It is also important to document the distance and relationship of the tumor with other anatomic landmarks, such as the ileocecal valve in ileocolic resection specimens, ampulla of Vater in pancreaticoduodenectomy specimens, etc.

6. If multiple tumors are present, assign a number to each tumor, describe and sample each tumor separately as shown in the Examples of Gross Description Using Paragraph System (section IV, example 2).

7. Examine the uninvolved intestine and mesenteric soft tissue, and describe any secondary pathology, such as changes of inflammatory bowel disease, ulcers, polyps, diverticulum, ischemic changes, etc.

8. Tissue banking: If there is an institution tissue bank protocol and/or a research protocol request for tissue samples, both tumor and adjacent normal small bowel mucosa are typically harvested according to the institutional tumor bank guidelines and the research protocol. Best effort from pathology should be made to harvest tissue as soon as possible to minimize the cold ischemia time for the best quality of banked tissue.

9. Photographs of the specimens and tumor may be taken as indicated or needed.

10. It is highly recommended that the specimen should be pinned out on a wax tablet and fixed in 10% buffered formalin overnight before grossing. If the resection is performed for metastatic disease, the specimen may be grossed the same day after a shorter period of fixation or without fixation. Please be aware that the quality of the sections would be suboptimal without fixation.

11. After overnight fixation, serial section each tumor at 3.0- to 5.0-mm intervals to identify the deepest invasion and measure the closest distance from tumor to the inked serosa and mesenteric resection margin. Take representative sections of the tumor as recommended below.

12. Carefully examine the mesenteric and/or pericolonic adipose tissue for possible lymph nodes and metastatic tumor nodules. If metastatic tumor nodules are identified in mesenteric adipose tissue, measure the distance of the tumor nodules from the closest mesenteric margin.

13. General recommendation for section submission:

a. Sections for margins: The proximal, distal, and mesenteric margins of the intestine are typically submitted en face if they are more than 3.0 cm from the tumor. If the tumor is within 3.0 cm from the margin, ink the margin and submit perpendicular sections of the margin with tumor if possible. Of note, all sections from the proximal and distal margins of small bowel or other sites of gastrointestinal tract should be full-thickness sections, not just the mucosa. If the surgeon designates the vascular pedicle margin, the vascular pedicle margin may be submitted en face as well.

b. Representative sections of the tumor: At least one representative section per centimeter of tumor size or five blocks from a primary tumor of small bowel should be submitted. These sections should include the area of deepest invasion to demonstrate the relationship of the tumor with subserosal and/or mesenteric soft tissue, the closest inked serosal surface (full thickness, cross-sections of the tumor), and radial margin; with adjacent normal small bowel mucosa; and with the other organs if present. If the resection is performed for large polyp(s) and grossly obvious invasive carcinoma is not identified, the entire polyp(s) should be submitted for histologic examination to rule out microscopic invasion. For a metastatic tumor

to the small bowel, the number of tumor sections can be reduced to two to three tumor sections per tumor.

c. Representative sections of all other lesions identified grossly (eg, ulcer, polyp, diverticula, fistula, etc) and uninvolved small bowel. If the uninvolved small bowel is grossly unremarkable, margin sections may be considered as a representative section of nonneoplastic small intestine and no additional section(s) from small bowel are required in such cases. However, in cases in which the small bowel is involved by inflammatory bowel disease (IBD), generous sampling of the nonneoplastic small bowel (one section every 5-10-cm interval along the intestine) is required to assess the severity of IBD and presence or absence of dysplasia.

d. Submit all possible lymph nodes: All grossly negative or equivocal lymph nodes are to be submitted entirely. Grossly positive lymph nodes may be partially submitted for microscopic confirmation of metastasis. There is no minimal number of lymph nodes for small bowel tumors, but the recent SEER data suggest that optimal staging may be achieved by examining at least five nodes for nonampullary duodenal adenocarcinoma and at least 10 for small intestine adenocarcinoma.[9]

II. Pancreaticoduodenectomy specimen for nonampullary neoplasms of the duodenum

Pancreaticoduodenectomy may be performed for adenocarcinoma or other types of carcinomas, well-differentiated neuroendocrine tumors, large adenomatous polyps, or other types of neoplasms in the periampullary region or other parts of the duodenum. Given the difference in pathologic staging, clinical management, and prognosis, it is important to differentiate duodenal adenocarcinoma from ampullary adenocarcinoma, pancreatic ductal adenocarcinoma, and distal common bile duct adenocarcinoma. Primary duodenal adenocarcinomas arising in periampullary region or other parts of duodenum often form mucosal-based polypoid or ulcerated mass but have no or only partial involvement of ampulla of Vater and may invades into pancreas (Figure 19-1). Only the carcinomas that center on the ampulla of Vater or demonstrate complete replacement of the ampulla of Vater should be classified as ampullary adenocarcinoma based on the current World Health Organization (WHO) criteria. In contrast, pancreatic ductal adenocarcinoma and adenocarcinoma of the distal common bile duct are centered in the pancreas or common bile duct and often have no or only focal involvement of duodenal mucosa or ampulla of Vater. Since there are significant overlaps in tumor morphology and immunohistochemical profile among these four different primary carcinomas, careful gross examination and accurate description of the tumor epicenter is the key for accurate classification of these tumors.

When gross pancreaticoduodenectomy for primary duodenal neoplasms, the same grossing protocol as that used for pancreaticoduodenectomy for pancreatic neoplasms should be used. Detailed description for specimen orientation, identification and evaluation of margin status, and gross examination, etc, have been described in the chapter on handling of the resection specimens, staging, and reporting of pancreatic exocrine and endocrine neoplasms. Specific details for grossing pancreaticoduodenectomy specimens for primary duodenal neoplasms include the following:

1. Carefully examine the mucosal lesion of the duodenum and measure tumor size in three dimensions. Document the tumor epicenter in the duodenum and its relationship with the ampulla of Vater. If the ampulla of Vater is not involved grossly by the tumor, document the distance of tumor to the ampulla of Vater.

2. Ink the serosal surface of the duodenum and the surface of peripancreatic soft tissue in the area of tumor.

3. After overnight fixation, serially section the tumor at 3- to 5-mm intervals, and describe the relationship of the tumor with the ampulla of Vater, pancreas, and distal common bile duct, and measure the distance from tumor to all the margins.

4. Carefully section the uninvolved pancreas and common bile duct at 3- to 5-mm intervals and document any possible lesion(s) in the pancreas and/or common bile duct.

5. Submission of the margins: All five resection margins, proximal gastric or duodenal margin, distal jejunal margin, pancreatic parenchymal margin, common bile duct/cystic duct margin, and uncinate/retroperitoneal margin, should be submitted. For duodenal neoplasms that are far (more than 3.0 mm) from the retroperitoneal margin, representative en face sections of retroperitoneal margin may be acceptable. However, submission of

the entire retroperitoneal margin perpendicularly may not only allow complete assessment of this margin and accurate measurement of the closest distance to the tumor, but also help to increase the yield in number of lymph nodes.

6. Representative sections of the tumor: At least one representative section per centimeter of tumor size or five blocks from the tumor should be submitted. The sections should sample the area of deepest invasion and document its relationship with the closest inked serosal surface (full-thickness sections of the tumor), ampulla of Vater, pancreas and distal common bile duct, adjacent duodenal mucosa, and other organs if present. If the pancreaticoduodenectomy was performed for large duodenal polyps, in which no invasive carcinoma is grossly identified, the entire polyp should be submitted for histologic examination to rule out microscopic invasion.

7. Representative sections of all other lesion(s) identified, including other mucosal lesion(s) and the lesion(s) located within pancreas or common bile duct, eg, ulcer, polyp.

8. Representative sections of uninvolved duodenal mucosa, ampulla of Vater, pancreas and common bile duct.

9. Submit all possible lymph nodes. A minimum of 12 lymph nodes is recommended for pancreaticoduodenectomy specimens.

III. Patch resection, transduodenal submucosal dissection, and endoscopic mucosal resection (EMR)

These types of resections can be performed for superficial and/or small nonampullary neoplasms of the duodenum with tumor size <1 cm. If the specimen orientation is provided, the margins should be inked in different colors to identify the proximal, distal, anterior/posterior or left lateral/right lateral margin, and deep margins or serosal surface. If the specimen is not orientated, ink the peripheral margin and deep margin/serosal surface in two different colors.

1. The specimen should be pinned to a wax tablet and fixed overnight.

2. Describe the lesion and measure the size of the lesion and the distance to all margins.

3. The specimen should be serially sectioned and entirely submitted as illustrated in Figure 19-3. Submit the two most peripheral sections away from the tumor (tips), inked side down, en face; then submit the remainder of the cross-sections sequentially on edge from one side to the other of the specimen, eg, from proximal to distal, from anterior to posterior, for histologic evaluation to accurately document the presence or absence of invasion, the depth of invasion, and the margin status

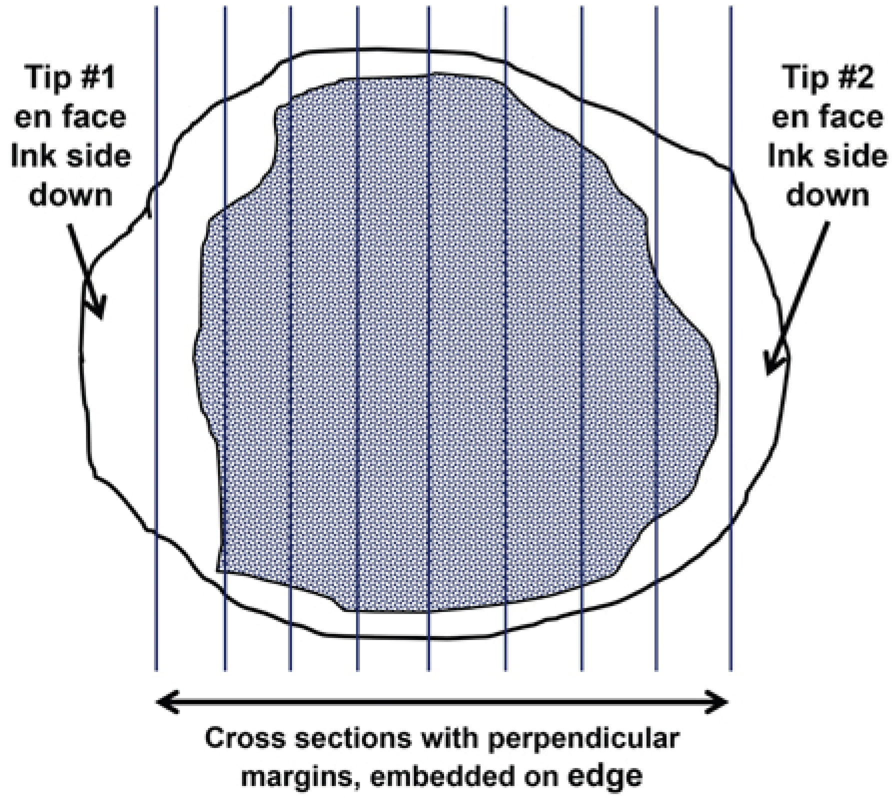

Figure 19-3. Schematic illustration of how to gross a patch resection, transduodenal submucosal dissection, or endoscopic mucosal resection (EMR) specimen.

IV Examples of gross description using the paragraph system[10]

Example 1. Gross description of pancreaticoduodenectomy for duodenal adenocarcinoma

A. HEAD OF PANCREAS, DISTAL STOMACH, DUODENUM, DISTAL COMMON BILE DUCT – A pancreatoduodenectomy specimen that includes the head of pancreas (6.0 x 5.5 x 4.0 cm), segment of common bile duct (4.8 cm in length and 0.6 cm in diameter), a portion of distal stomach (10.0 cm in length along the great curvature and 8.8 cm in circumference at proximal margin), duodenum and jejunum (19.0 cm in length and 2.8 cm in circumference at distal margin), and perigastric adipose tissue along the greater curvature of stomach (9.0 x 3.5 x 3.0 cm).

A polypoid, ulcerated mass is identified in the duodenum. The tumor measures 3.8 x 2.8 x 2.5 cm and is located 1.8 cm distal to the ampulla of Vater. The cut surface of the mass is tan-white, solid, and firm with no obvious necrosis or hemorrhage. Grossly the tumor invades through muscularis propria into the periduodenal soft tissue but does not involve ampulla of Vater, common bile duct, or pancreas. The tumor is 16.0 cm from distal small bowel margin, 15.0 cm from proximal gastric margin, 5.0 cm from pancreatic margin, 5.0 cm from common bile duct margin and 3.0 cm from closest retroperitoneal margin.

Common bile duct and pancreatic duct are probe patent and open into the ampulla. Both ducts are not dilated. The ampulla of Vater, pancreas, and common bile duct appear normal grossly. The gastric and rest of duodenal mucosa shows focal mild nodularity and are otherwise grossly unremarkable. Distal portion of the small bowel (10.5 cm in length) shows ischemic change and appears dusky. Twenty-one possible lymph nodes are identified in the peripancreatic and perigastric soft tissue. A portion of tumor, normal duodenal mucosa, and normal pancreas have been submitted for tumor banking.

Ink code

Uncinate/retroperitoneal margin - black

Serosal surface of the duodenum in the area of tumor - blue.

Section code

A1: Common bile duct margin, en face for frozen section diagnosis and permanent section

A2-A3: Pancreatic resection margin en face, for frozen section diagnosis and permanent section

A4: Representative section of proximal gastric margin, en face
A5: Distal small bowel margin, en face
A6-A10: Uncinate/retroperitoneal margin, perpendicular sections, entirely submitted
A11-A12: Tumor in relation to the ampulla and common bile duct
A13-A15: Tumor in relation to pancreas and peripancreatic soft tissue
A16-A18: Additional sections from the tumor and adjacent duodenal mucosa
A19: Representative section of pancreas with pancreatic duct
A20: Representative section of pancreas with common bile duct
A21: Representative section of stomach
A22: Representative section of the duodenum with mucosal nodularity
A23: Five possible peripancreatic lymph nodes
A24: Four possible peripancreatic lymph nodes
A25-A26: Three possible peripancreatic lymph nodes in each cassette
A27: One possible perigastric lymph node, bisected entirely submitted
A28: Five possible perigastric lymph nodes

Example 2. Gross description of segmental resection of small bowel

A. ILEUM, SEGMENTAL RESECTION – The specimen consists of a segment of small bowel (22.8 cm in length, 3.0 cm in circumference at proximal margin and 2.8 cm in circumference at distal margin) and attached mesenteric adipose tissue (22.0 x 5.0 x 3.5 cm). There is a black stitch attached to one end of the small bowel, which marks the proximal resection margin.

Two separate tumors are identified on the mucosal surface of small bowel. Tumor #1 is an ulcerated mass measuring 3.0 x 2.6 x 1.5 cm and is located at 12.0 cm from proximal margin, 8.0 cm from distal margin, and 3.0 cm from the mesenteric resection margin. The cut surface of this tumor is yellow-tan with focal area of fibrosis and hemorrhage. Grossly this tumor invades through the muscular wall into the mesenteric adipose tissue but does not involve the serosal surface. Tumor #2 is a polypoid mass measuring 1.8 x 1.5 x 1.1 cm. Tumor #2 is located at 3.5 cm proximal to tumor #1, 8.5 cm from proximal margin, 12.3 cm from distal margin, and 5.0 cm from the mesenteric resection margin. The cut surface of the second tumor is similar to tumor #1. The second tumor grossly invades into the muscularis propria but has no involvement of the mesenteric adipose tissue or subserosal soft tissue. A 4.0 x 3.5 x 3.5 cm mass is also identified in the mesenteric adipose tissue. The cut surface of mesenteric mass is yellow-tan with focal area of calcification and hemorrhage. The mesenteric mass is grossly 0.8 cm from the closest mesenteric resection and 11.0 cm from both proximal and distal small bowel resection margins.

The rest of the small bowel is grossly unremarkable. Twelve possible lymph nodes are identified in the mesenteric adipose tissue. A portion of tumor and normal small bowel mucosa have been submitted for tumor banking.

Ink code

Serosa overlying tumor #1 - black
Serosa overlying tumor #2 - blue
Mesenteric margin - red

Section code

A1: Proximal margin, en face
A2: Distal margin, en face
A3-A4: Representative sections of closest mesenteric margin with mesenteric tumor, perpendicular sections
A5-A9: Representative sections from tumor #1 with serosal surface and mesenteric adipose tissue
A10-A14: Representative sections from tumor #2 with serosal surface and mesenteric adipose tissue
A15-A17: Representative sections from mesenteric mass
A18: Representative section of normal small bowel
A19-A21: Four possible lymph nodes in each cassette

V. Grading of well-differentiated neuroendocrine tumor of small bowel, other parts of gastrointestinal tract, and pancreas

According to the WHO grading system, well-differentiated neuroendocrine tumors of small bowel, other parts of gastrointestinal tract, and pancreas are classified into G1, G2 and G3 based on the mitotic rate per 2 mm^2 in the most mitotically active area of the tumor (hot spot) and/or Ki-67 labeling index in the tumor area with highest nuclear labeling for Ki-67 (hot spot).

G1 well-differentiated neuroendocrine tumor: <2 mitosis per 2 mm^2 and/or a Ki-67 index of <3%

G2 well-differentiated neuroendocrine tumor: 2-20 mitosis per 2 mm^2 and/or a Ki-67 index of 3–20%

G3 well-differentiated neuroendocrine tumor: >20 mitosis per 2 mm^2 and/or a Ki-67 index of >20%

It is proposed that the mitotic count should be performed in at least 10 mm^2 in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Although the precise method of assessment of Ki-67 labeling index has not been standardized, eye-balling can be used for most tumors; however, for tumors with Ki-67 index close to the grade cut-off values, it is recommended to perform the manual count on the print of camera-captured image of the hot spot or quantitative image analysis. It has been recommended that a minimum of 500 tumor nuclei be counted to accurately determine the Ki-67 index. When there is a discrepancy between the mitotic count and Ki-67 index in a given tumor, the tumor should be assigned a higher grade based on the higher value of those two parameters. Representative micrographs of a G2 well-differentiated neuroendocrine tumor of the ileum are shown in Figure 19-4. Functioning tumors are those associated with clinical manifestations of hormone production or secretion of measurable amounts of active hormone; immunohistochemical demonstration of hormone production is not equivalent to clinically apparent functionality.

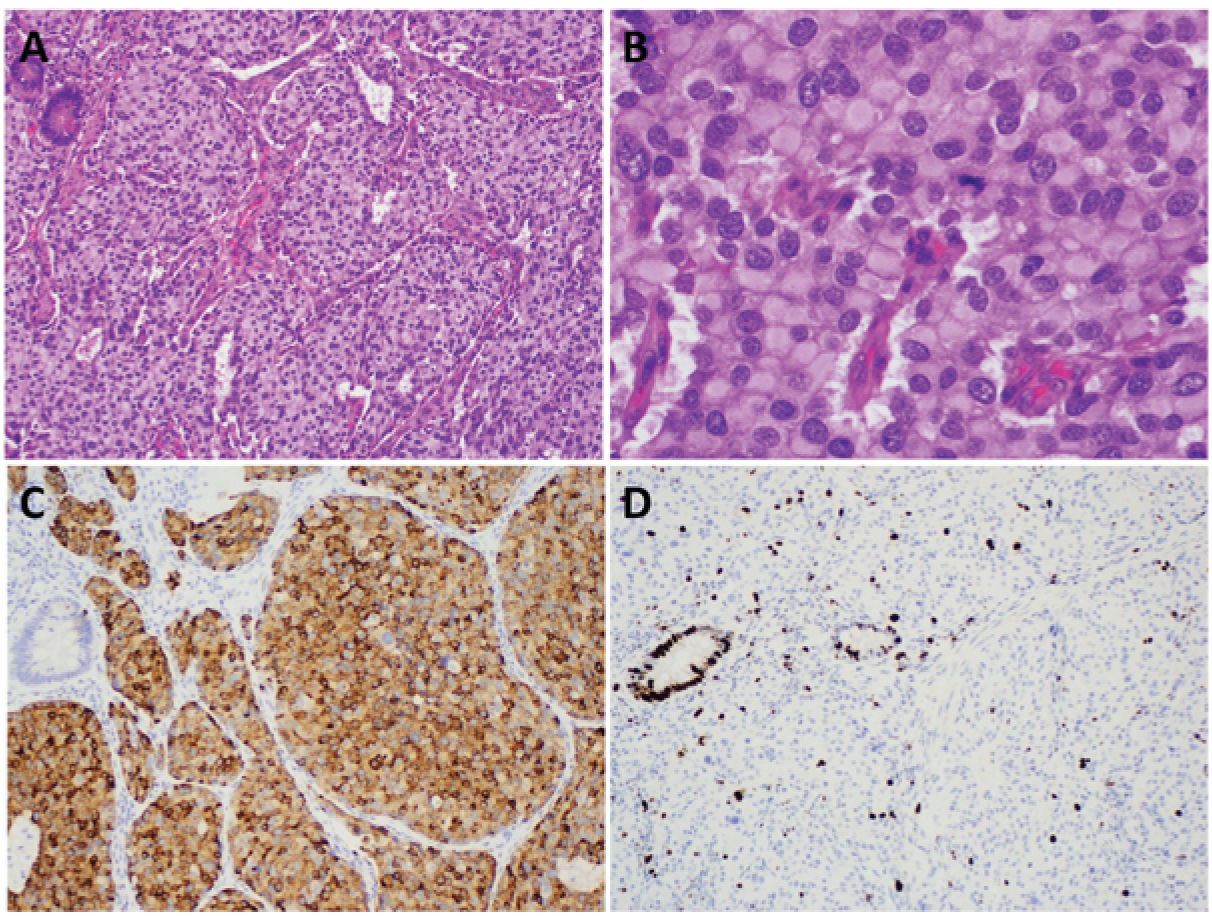

Figure 19-4. A, B. A well-differentiated neuroendocrine tumor of the ileum that is positive for chromogranin (C) and has a Ki-67 labeling index of approximately 5% (D) and 4 mitosis per 2 mm^2 (G2) (magnification: A, D, 40x; B, 200x, C, 100 x).

For poorly differentiated (high-grade) neuroendocrine carcinomas, which typically have >20 mitosis per 2 mm^2 and a Ki-67 index of >20%, the CAP protocol for carcinoma of the corresponding organ of the gastrointestinal tract or pancreas should be used.

VI. What to include in the synoptic pathology report

The synoptic pathology reports for small bowel neoplasms recommended by the CAP include the following information that is required for appropriate tumor staging and patient care.

- Procedure: Segmental resection, ileocolic resection, pancreaticoduodenectomy (Whipple resection), or other (specify).
- Tumor site: Duodenum, jejunum, ileum, small intestine not otherwise specified, or other (specify).
- Tumor size: Greatest dimension: __ cm and additional dimensions: __x__ cm
- Macroscopic tumor perforation: Not present, present, or cannot be determined.
- Histologic type using the WHO classification of small intestinal neoplasms.
- Histologic grade based on the corresponding WHO grading system for carcinomas, neuroendocrine tumors, or gastrointestinal stromal tumor.
- For well-differentiated neuroendocrine tumors, tumor focality (unifocal, multifocal [specify the number of tumors], or cannot be determined); mitotic rates, Ki-67 labeling index, and histologic subtype of neuroendocrine tumor should also be included in the synoptic pathology report using the schemes described in the current CAP cancer protocol for neuroendocrine tumors of small bowel and duodenum.
- Tumor extension (T stage): Representative micrographs showing tumor invasion into submucosa, muscularis propria, periduodendual soft tissue, or through the serosa as shown in Figure 19-5.
- Margin status: Uninvolved by invasive carcinoma, involved by invasive carcinoma, or cannot be assessed. Presence or absence of adenoma or high-grade dysplasia at the distal or proximal resection margins should also be documented in the pathology report. Of note, the mesenteric margin/radial margin is considered positive if the tumor is present within 0 to 1 mm from the margin.
- Lymphovascular invasion: Not identified, present, or cannot be determined.
- Perineural invasion: Not identified, present, or cannot be determined.
- Regional lymph nodes: Number of lymph nodes examined and number of lymph nodes involved.
- Additional pathologic findings: Adenoma(s) or other type(s) of polyps, Crohn’s disease, celiac disease, mesenteric tumor deposits, other (specify), or none identified, etc.
- Ancillary studies: Describe the results of molecular testing and immunohistochemistry for mismatch repair proteins and other cancer biomarker testing.
- Pathologic stage classification: primary tumor (pT), regional lymph nodes (pN), and distant metastasis (pM) classification based on the AJCC 8th edition staging manual.

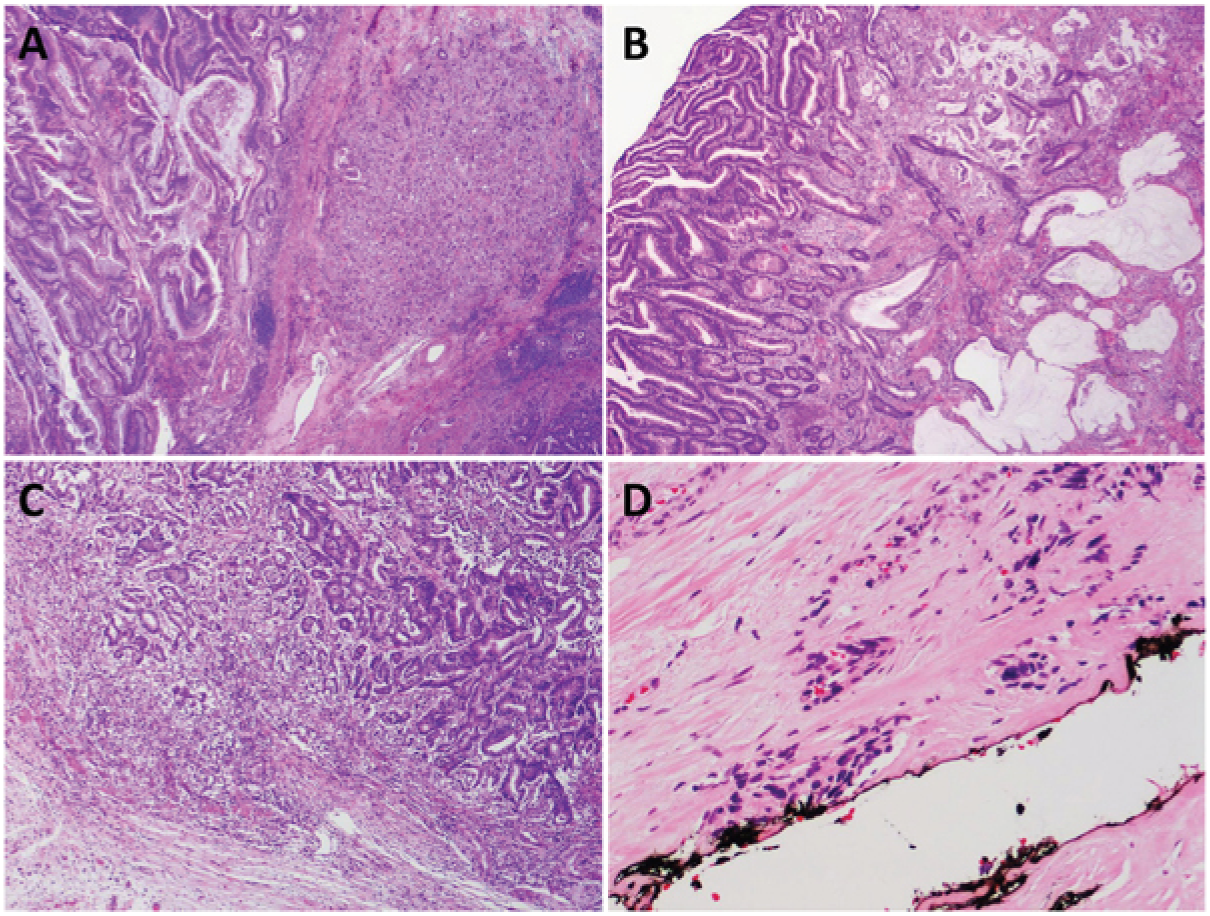

Figure 19-5. A. Poorly differentiated duodenal adenocarcinoma invading into submucosa arising in a tubulovillous adenoma. B. Moderately differentiated mucinous adenocarcinoma invading into the muscularis propria arising in a tubulovillous adenoma of the duodenum. C. Moderately differentiated adenocarcinoma invades through muscularis propria of duodenum into periduodenal soft tissue. D. Adenocarcinoma is present at the inked serosal surface (magnification: A-D, 40x).

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20. Stomach

Laura H. Tang, MD, PhD

Introduction

Gastrectomy specimens include partial (usually distal stomach) and total resection of the stomach commonly for epithelial neoplasms, ie, carcinoma and neuroendocrine tumor (carcinoid), as well as mesenchymal tumors and rare nonneoplastic conditions. Small and localized lesions may be removed by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), which comprises a fragment of flat and superficial gastric mucosa. In order to handle the specimens appropriately and provide adequate and accurate information for pathologic staging and therapeutic decisions, it is prudent for pathologists to understand the clinical workup and management of specific diseases. This chapter will focus on stomach resections primarily for gastric cancers.

I. Clinical workup for gastric cancer

Following the initial diagnosis of gastric cancer on an endoscopic biopsy, subsequent clinical staging procedures include an endoscopic ultrasound (EUS) and computed tomography (CT) or positron emission tomography (PET)-CT to assess the depth of tumor invasion into the gastric wall (T), locoregional lymph node involvement (N), and potential distant metastasis (M) (Figure 20-1). The clinical evaluation of T and N stage by these modalities is relatively robust with accuracy in the range of 70% to 90%.[1,2] In addition, both EUS and CT allow for image-guided fine-needle aspiration of suspicious extraluminal nodules (usually lymph nodes) or distant masses. At the time of EUS, an additional biopsy of the primary tumor may be obtained to confirm the diagnosis and for additional biomarker testing (such as HER2Neu, DNA mismatch proteins, PDL-1, etc) or for molecular testing (next-generation sequencing) if it is clinically indicated.[3,4]

Based upon these evaluations, the clinical stage of the tumor and therapeutic strategies are then determined (Figure 20-1).[5] Patients who presented with localized and early stage disease (T1/T2N0M0) will proceed with surgery. For those who presented with locally advanced disease (T3N0M0 or TanyNpostiveM0) are offered neoadjuvant therapy followed by surgery. A subset of patients in the latter group may undergo additional laparoscopy to identify potentially occult metastatic disease (M1). At the time of laparoscopy, peritoneal washings and peritoneal biopsies are usually submitted for cytologic and histologic evaluation, respectively. Patients with negative peritoneal metastasis will proceed with neoadjuvant treatment followed by surgery. Patients with evidence of metastatic disease including occult peritoneal metastasis are only offered chemotherapy and usually have unfavorable outcome.[6,7]

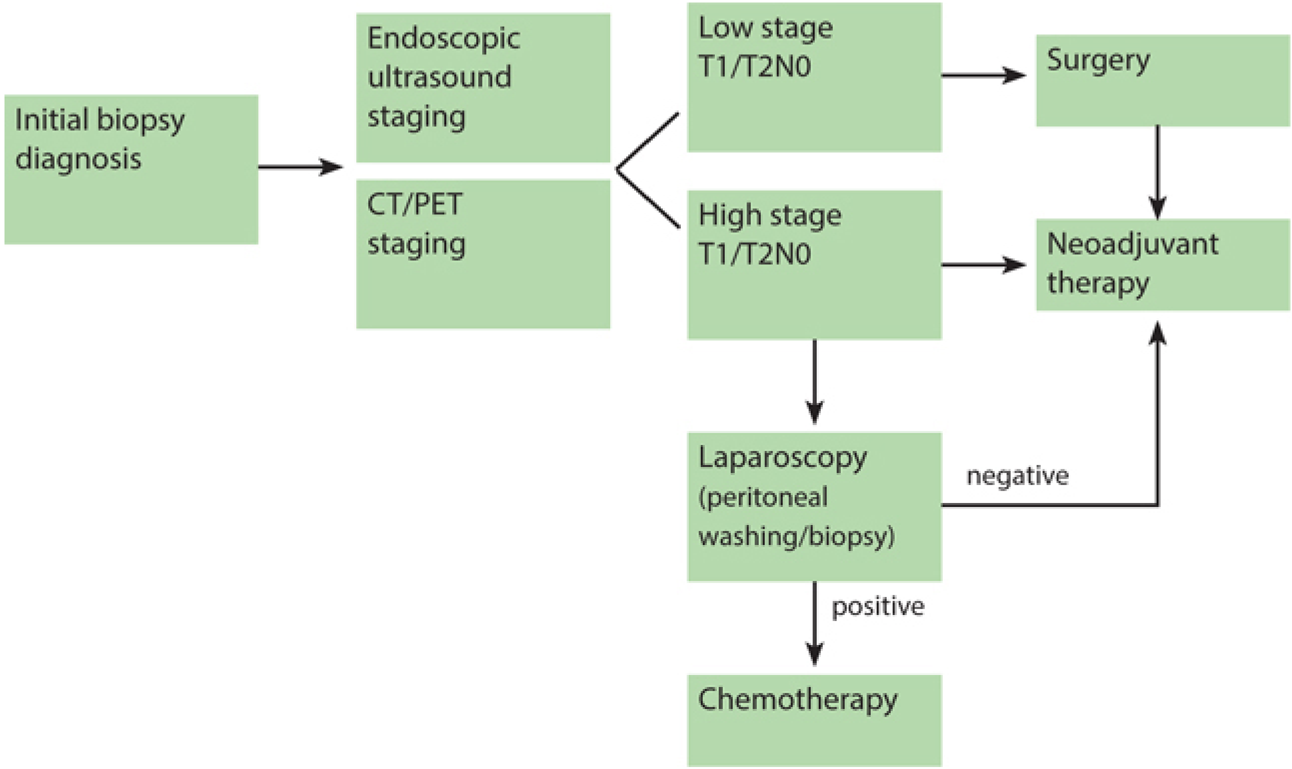

Figure 20-1. Clinical staging and therapeutic strategies for gastric cancer.

II. Clinical indications for the type of surgery

1. Endoscopic mucosal resection or submucosal dissection (EMR/ESD)

Mucosal resection of gastric carcinoma or carcinoid tumors can be achieved by either endoscopic mucosal resection or endoscopic submucosal dissection for isolated and early gastric cancers. The guidelines for indication of EMR are (1) well- or moderately differentiated adenocarcinoma or papillary histologic subtypes, (2) nonulcerative lesion and a depth of invasion that is confined to the mucosa (stage Tis or T1a), (3) a tumor diameter of ≤20 mm, and (4) absence of lymphatic-vascular invasion on initial biopsy. ESD can be performed on larger tumors (>20 mm and ≤30 mm) without ulcer and with invasion into superficial submucosa (<1/3 depth of submucosa) (stage T1b).[8,9] Endoscopic mucosal resection and submucosal dissection are not indicated for poorly differentiated adenocarcinoma or signet-ring cell carcinoma.

2. Proximal gastrectomy

Gastric cancer located in the cardia without involvement of gastroesophageal junction (GEJ) could be resected with proximal gastrectomy; however, this may not be commonly performed due to a higher rate of complications including gastric reflux and issues concerning an adequate proximal margin clearance.[10] Thus, total gastrectomy may be performed for the proximal cancer (Figure 20-2A). If the tumor is in the proximity or straddles the GEJ, esophagogastrectomy may be preferred from the chest by thoracic surgeons (see esophageal chapter).

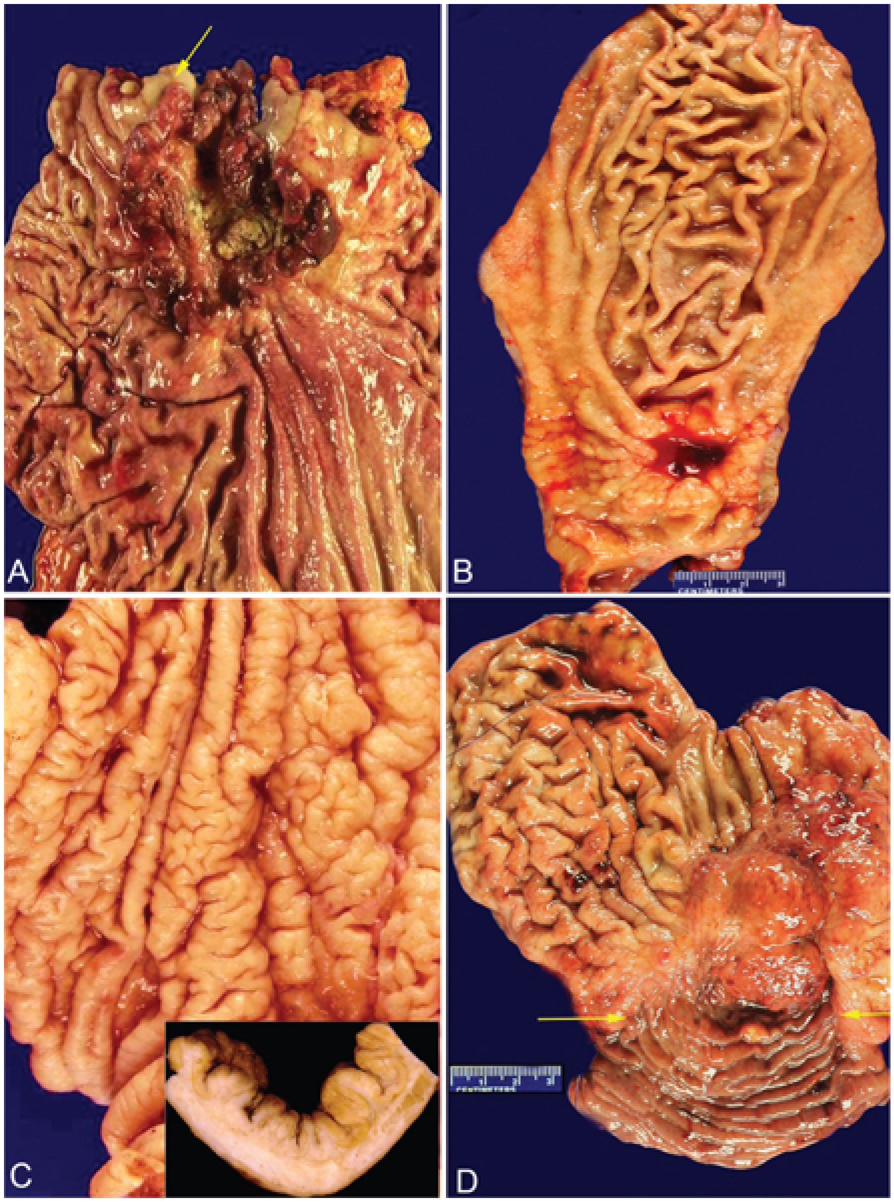

Figure 20-2. Gross pathology of gastric adenocarcinoma. A. A proximally located gastric adenocarcinoma with minimal extension into the squamous mucosa (arrows) of the esophagus. B. An ulcerated carcinoma located in the distal stomach. C. A diffuse type adenocarcinoma located in the body of the stomach with intact mucosa but rigid mucosal fold. A cross-section of the mucosa reveals thickened gastric wall secondary to diffuse infiltration by tumor cells. D. A remnant gastric cacumina located in the gastric mucosa near the anastomotic line (arrows).

3. Distal/subtotal gastrectomy

The antrum is the most common location for gastric adenocarcinoma (Figure 20-2B) which may involve the pylorus and the body of the stomach distally and proximally, respectively, when the tumor is large. Distal or subtotal gastrectomy is performed by either open or laproscopic/robotic procedure with Billroth-I, Billroth-II, or Roux-en-Y reconstruction.[10]

4. Completion gastrectomy

Carcinoma in the remnant stomach can present as a primary cancer following partial gastrectomy for a benign disease such as ulcers, which may occur with a protracted interval of more than a decade, as well as metachronous cancer following partial gastrectomy for gastric adenocarcinoma. Completion gastrectomy may be indicated after clinical staging and evaluation (Figure 20-1). The specimen includes the remnant stomach and gastrojejunostomy.[11] The remnant cancer is almost always found in the gastric mucosa near the anatomic site (Figure 20-2D).

5. Total gastrectomy

As indicated above, proximal gastric cancer may be resected with total gastrectomy due to technical issues of surgery. Pure Lauren's diffuse type gastric cancer is uncommon, which usually originates in the body of the stomach. Classic diffuse gastric adenocarcinoma can involve the entire stomach without an apparent ulcerated/mass lesion on the mucosal surface and present as linitis plastica (Figure 20-2C). Unless the tumor is present at an early stage and localized, total gastrectomy is performed for diffuse gastric cancer.[10]

Hereditary diffuse gastric cancer (HDGC) is a genetic cancer susceptibility syndrome with inactivating germline mutations in the E-cadherin gene *CDH1*. Initially identified in three Maori families in New Zealand, many more families throughout the world have been reported to carry the CDH1 germline mutation.[12] The disease penetrance is relatively high (70–80%) with a lifetime risk of developing gastric cancer of approximately 67% in men and 83% in women.[13] Due to inadequacy of clinical screening and poor outcome, prophylactic total gastrectomy is recommended for asymptomatic *CDH1* mutation carriers. Most specimens have multiple foci of superficial diffuse signet-ring cell cancer including patients who have undergone extensive clinical screenings with benign gastric biopsies.[14] Since the cancer is multifocal and distributed throughout the entire stomach, prophylactic gastrectomy must include the entire stomach.

In uncommon situations, total gastrectomy may be performed in cases of familial or nonfamilial polyposis syndromes and Menetrier's hypertrophic gastropathy in symptomatic patients with gastrointestinal bleeding and hypoalbuminemia, or concerns for potential malignant transformation (Figure 20-3).

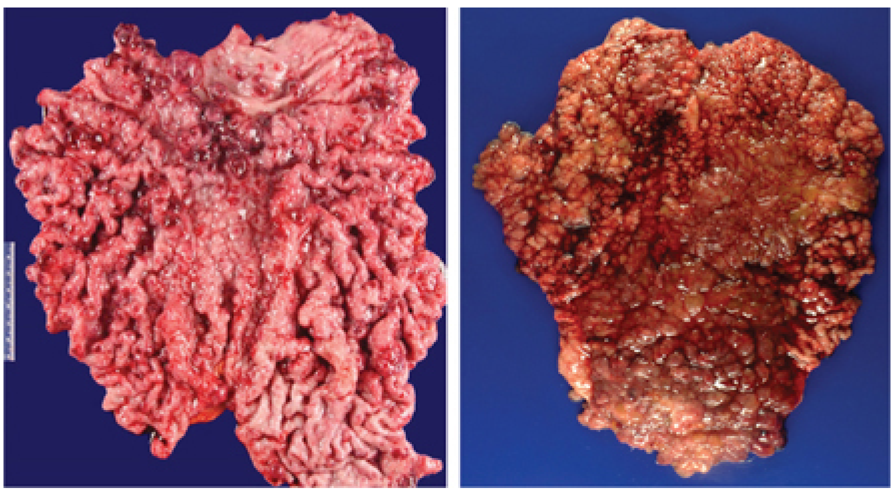

Figure 20-3. Gross photos of total gastrectomy performed for diffuse polyposis (right) and Menetrier disease (left).

6. Lymphadenectomy

Partial and total gastrectomy may be accompanied with either D1 or D2 lymphadenectomy from these operations.[15] D1 lymph nodes include most perigastric lymph nodes (stations 1–6), which are usually attached to the gastrectomy specimen; whereas D2 dissection is performed by the surgeon and submitted as separate parts, which comprises additional nodes from left gastric artery (station 7), common hepatic artery (station 8), celiac axis (station 9), splenic hilum (station 10), splenic artery (station 11), and proper hepatic artery (station 12) (Figure 20-4). Both D1 and D2 lymph node groups are considered as local regional nodes, and carcinoma identified outside this field is considered as distant metastatic disease (M1). D2 lymphadenectomy is the standard lymphadenectomy performed in high-incidence countries such as Japan and Korea, and less extensive lymphadenectomies are often performed in lower incidence countries such as the Unites States.

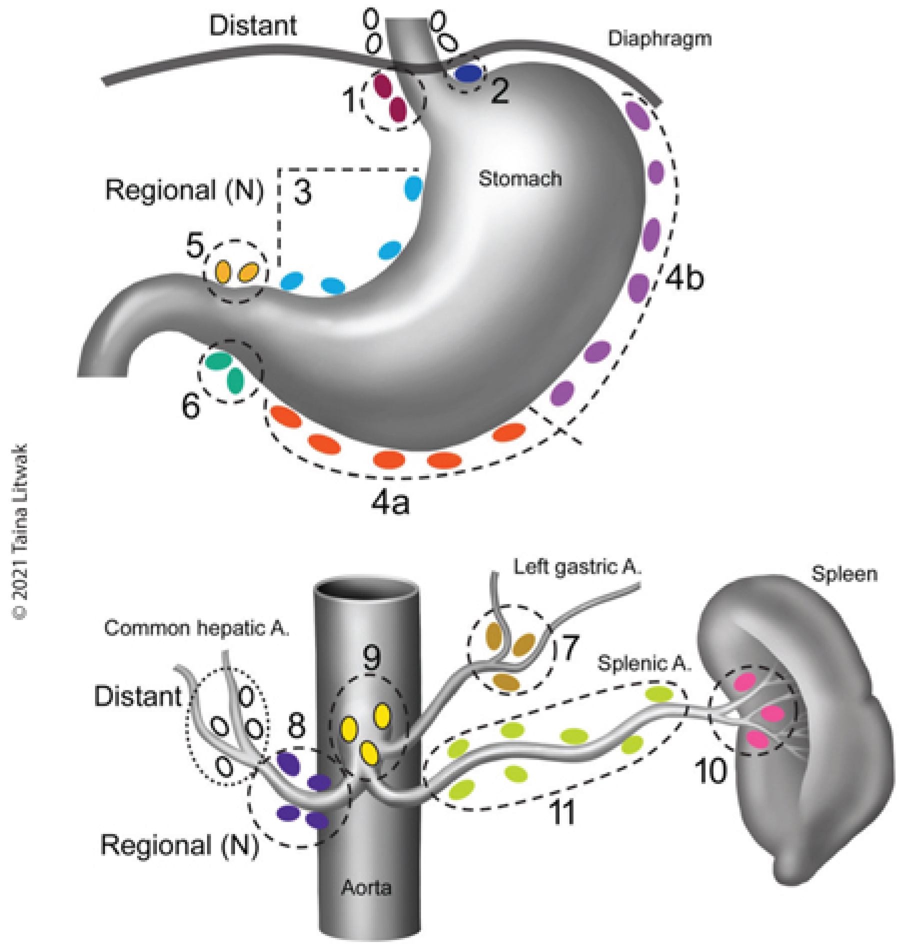

Figure 20-4. D1 and D1 lymphadenectomy associated with gastrectomy for gastric cancer.

III. Gross examination and prosection

1. Endoscopic mucosal resection and endoscopic submucosal dissection specimens

This specimen usually consists a circular or semicircular fragment of flat mucosa that is pinned on a Styrofoam or cork board provided with the orientation (Figure 20-5). Upon examination of the specimen, a gross photograph should be taken before thorough fixation in formalin for several hours or overnight. Additional photographs may be necessary after fixation if the lesion is better appreciated than that in the fresh specimen. The size, color, and configuration of the lesion should be described as well as the closest margin clearance. Ink should be applied to the margins of the specimen according to the orientations provided. If the margin clearance from all mucosal edges is grossly adequate (>0.5 cm from the lesion), the closest margin and its opposing margin can be submitted en face, and the rest of the specimen can then be serially and evenly sectioned in 2- to 3-mm thickness and submitted entirely (Figure 20-6A). However, if the tumor is close to the mucosal margin (<0.5 cm clearance), this margin should be submitted in sections perpendicular to the lesion (Figure 20-6B).

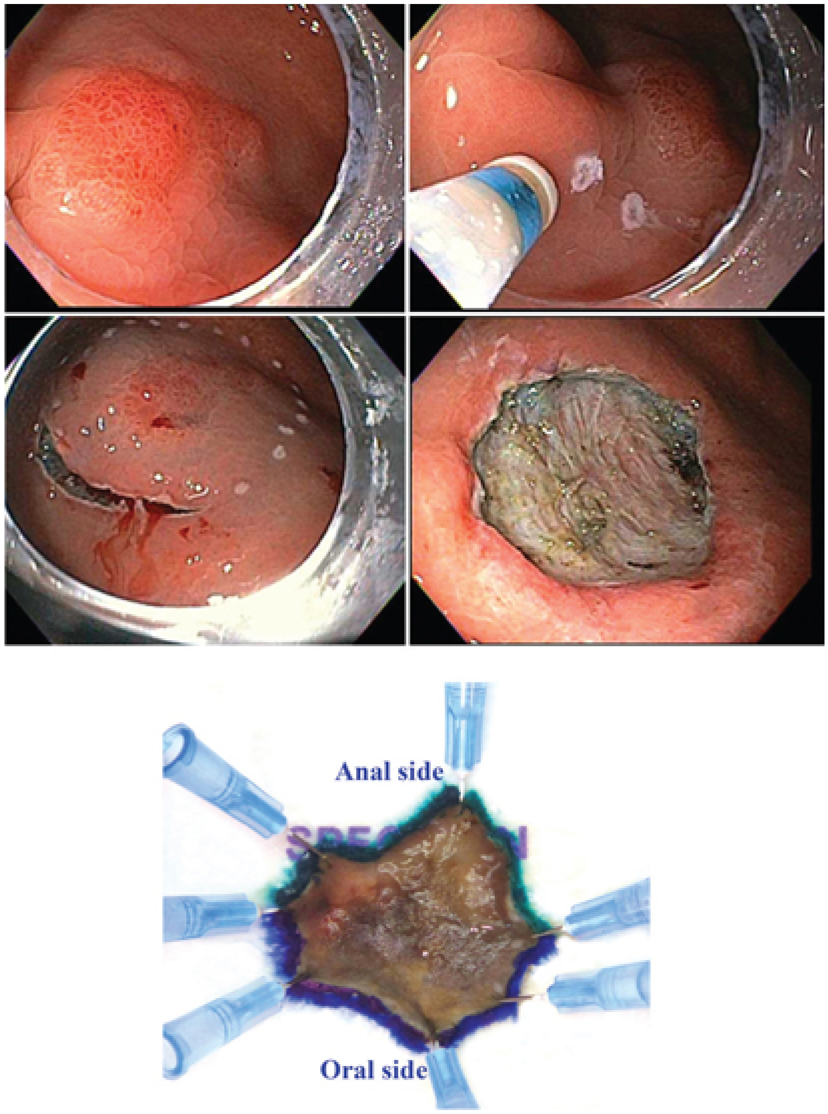

Figure 20-5. Endoscopic mucosal resection (EMR) of a gastric lesion. Endoscopic mucosal resection procedure (top 4 panel anticlockwise). EMR specimen (bottom panel) with mucosal edge inked blue (oral side) and green (anal side), respectively according to the orientation provided.

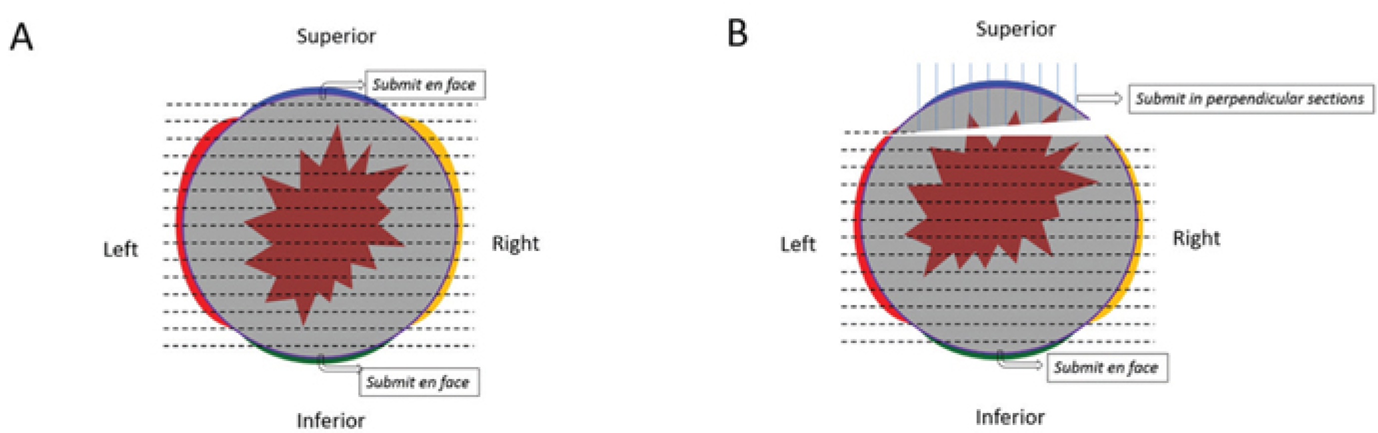

Figure 20-6. Illustration of prosection of endoscopic mucosal resection/dissection (EMR/EMD) specimen. A. The closest margin and its opposing margin should be submitted en face when the gross clearance is >0.5 cm. B. Perpendicular sections of the closest margin should be submitted when the gross clearance is <0.5 cm.

2. Gastrectomy specimen for cancer

The specimen is usually received fresh and unopened, and may consist of total, subtotal, or partial gastrectomy with or without attached omentum and gastrocolic and/or gastrohepatic adipose tissues. The dimensions of the specimen should be measured along greater and lesser curvatures, respectively. The prosector should pay specific attention to any attached tissues or organs (or portions thereof) including diaphragm, spleen, pancreas, large bowel, etc, before applying ink to the specimen. These attachments can be small and may or may not be designated by the surgeon with a suture or ink, and they may be impossible to recognize when covered by ink.

Upon palpation, the location of the tumor may be identified before opening, and the outside surface (usually serosa) overlying the deep aspect of the tumor should be inked. For tumors of proximal location that involve the gastroesophageal junction, esophageal adventitia should be inked, which would be a resection margin should this site be involved by tumor.

The preferred site to open the specimen is the greater curve unless the tumor is large and occupies most of greater curve; in such situation, the specimen should be opened from the lesser curvature. One should try to avoid cutting through a noncircumferential tumor. The tumor should be measured in three dimensions. The exact location (cardia, fundus, body, or antrum; anterior wall or posterior wall; greater curvature or lesser curvature) should be specified. The distances of the tumor from the proximal and distal margin should also be measured. The gross configuration of the tumor should be described as superficial (grossly limited to the mucosa and submucosa), polypoid or exophytic, ulcerated, fungating with raised edges, etc.

The opened specimen should then be fixed in formalin for 4 to 5 hours or overnight for optimal orientation. In cases of status post neoadjuvant therapy, the gross lesion may not be apparent on the initial examination, but a scar-like tumor bed could be better appreciated after fixation. Upon sectioning of the tumor, the depth of tumor invasion should be estimated and described (ie, mucosa, submucosa, muscularis propria, subserosa, serosa or beyond, with or without perforation).

The tumor should be sectioned at 4- to 5-mm interval for thorough gross examination, and at least two to three tumor sections with the deepest gross invasion should be submitted for histopathology evaluation, including portions of attached adipose tissues, if involved. The relationship of the deepest invasive tumor to the inked serosal surface or peritoneum should be represented in these sections. Additional sections should be submitted if the tumor is large or heterogeneous in appearance (approximately one section of every centimeter of the tumor). Some of these sections should include the transition between the tumor and the adjacent uninvolved mucosa. In cases when additional tissue or other organs are attached to the gastrectomy, their relationship to the tumor should be documented in both the gross description and in sections submitted for histopathology. In specimens of status post neoadjuvant treatment that reveal profound gross treatment effect, the entire scar-like tumor bed should be sampled for histopathology evaluation. Any other serosal nodules and peritoneal deposits in the specimen should be sampled and their relationship to the primary tumor should be documented.

The remaining gastric, duodenal, and esophageal mucosa (if present) without involvement by the tumor should also be described as without or with abnormalities (such as erythema, atrophy, polyps, abnormal folds, etc) and representative sections submitted. The proximal and distal resection margins, if they have not already been submitted for intraoperative frozen section evaluation, should be entirely submitted en face (with a clearance of >2.0 cm) or perpendicularly (with a clearance of <2.0 cm) in the area close to the tumor and en face for the rest of the margin.

If D1 or D2 lymphadenectomy is performed, lymph node groups may be submitted separately (particularly for D2 dissection) from the gastrectomy specimen and stations designated by the surgeon (Figure 20-2). These specimens are usually submitted entirely for histopathology unless the majority of the specimen is composed of fat, larger than 10 cm in size, and there are no identifiable lymph nodes; in such cases three to four representative sections for each part should be adequate. If perigastric lymph nodes are not dissected by the surgeon and come with the gastrectomy specimen, a though examination of the specimen is critical to identify and submit all possible lymph nodes. At least 15 nodes are required for adequate staging. If gross lymph node metastasis is evident, the size of the largest positive lymph node should be recorded.

3. Gastrectomy specimen for prophylaxis (CDH1-associated hereditary gastric cancer)

Germline mutations in *CDH1* gene are the molecular basis for familial gastric cancer syndrome, and prophylactic total gastrectomy is often considered after an establishment of the diagnosis.[16] Patients, typically undergo multiple prior endoscopic procedures for the identification of occult and early signet-ring cell carcinoma. However, the decision to pursue total gastrectomy may be determined even in the absence of carcinoma in biopsies.[14]

The stomach should be opened from greater curve for the optimal viewing and mapping (Figure 20-7). The mucosa is usually unremarkable (even in the evidence of microscopic foci of early carcinoma); but it may have changes consistent with prior biopsy sites. It is important to document the presence or absence of esophageal squamous mucosa at the proximal margin and duodenal mucosa at the distal resection margin, respectively, unless the margin status has already been assessed at the time of intraoperative frozen sections (see section IV). Any gastric mucosa left behind in the patient is subjective to the development of diffuse gastric carcinoma. The specimen is then mapped in five regions (cardia, anterior and posterior fundus/body, anterior and posterior distal body/pylorus, respectively) (Figure 20-7) with further designations by numbers within each region.[17] It is recommended that approximately one-third of the mucosa be submitted from each of the five regions for the initial histopathology evaluation. If no signet-ring cell carcinoma is identified, an additional one-third, and then the rest of gastric mucosa should be subsequently submitted. However, some may prefer to submit the entire gastric mucosa in one batch initially.

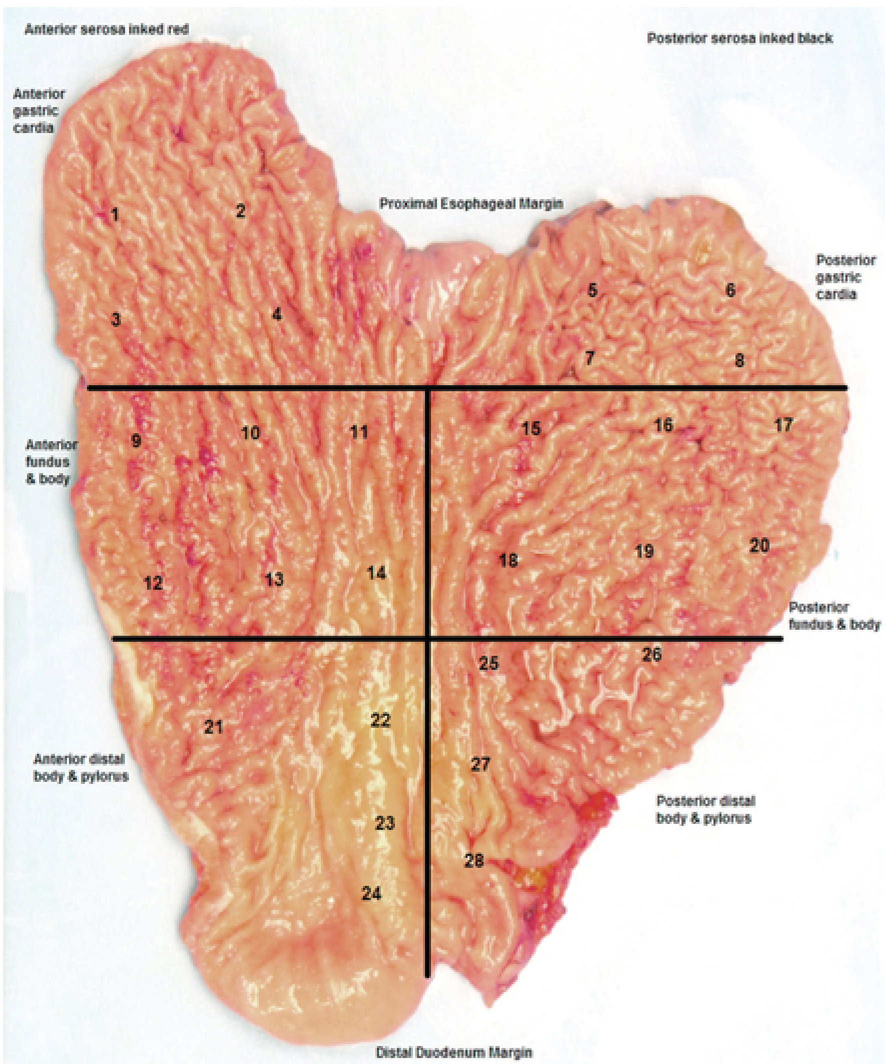

Figure 20-7. Mapping of gastric mucosa of a total gastrectomy performed for CDH1-associated hereditary diffuse gastric carcinoma.

4. Gross description template for gastrectomy (sample)

The specimen is received fresh and is labeled with the patient's name and "distal gastrectomy (partial gastrectomy/total gastrectomy)". It consists of a portion of a stomach with attached adipose tissue and omentum. The stomach measures 12.0 cm along the greater curve, 10.0 cm along the lesser curve, and 5.0 cm in its widest diameter. It has a pink tan smooth serosal surface. On the serosal surface is a focally irregular (puckered/perforated) area with discoloration at the opposing site of the palpable tumor and this area is inked. The attached omentum measures 18.0 x 8.0 cm and is grossly unremarkable (involved by cancer as 3 tumor deposits).

The specimen is opened along the greater (lesser curvature) to reveal a tan (brown/red) tumor mass with an exophytic (polypoid / ulcerated with raised borders / fungating configuration; or a scar-like lesion--status post neoadjuvant therapy). The tumor is 2 cm from the proximal margin and 10 cm from the distal margin. The (representative) proximal and the (representative) distal resection margins were submitted during the intraoperative frozen section examination; and the remaining margins are entirely submitted en face. The tumor measures 3 cm in length and 2.5 cm in width. Sectioning of the tumor reveals a 0.9 cm depth of invasion. Gross tumor perforation is absent (present). Sectioning of the tumor reveals it is grossly confined to the mucosa (it invades into the submucosa, the muscularis propria, subserosa / it penetrates the serosa and invades the attached structure/organ). The remaining gastric mucosa is unremarkable (or shows atrophy/erythema/polyps).

Multiple lymph nodes are identified in the perigastric adipose tissue, measuring from 0.5 cm to 2.0 cm in greatest dimension. All identified lymph nodes are submitted. Representative sections of the tumor and gastric mucosa are summitted.

Summary of sections

PM - proximal margin

DM - distal margin

U - uninvolved gastric mucosa

T – tumor or tumor bed

Pol - polyp

O - omentum

LN - whole lymph nodes

BLN - bisected lymph nodes

IV. Intraoperative margin assessment

Resection margins are among the strongest predictors of cancer-related mortality for gastric adenocarcinoma. An intraoperative consultation with a pathologist, including a frozen section of the specimen to microscopically assess the margin status, offers an opportunity to modify surgical management with the goal of achieving an R0 resection. Intraoperative assessment of distal resection margin for gastrectomy is less common since the surgeon usually takes adequate clearance of the duodenum without compromising the ampulla. The frozen section interpretation of the proximal margin deserves special attention since this is where most errors occur.[18] Importantly, diffuse signet-ring cell cancer constitutes >80 % of the false-negative readings.[19]

When assessing the proximal resection margin in a total gastrectomy with the inclusion of a portion of distal esophagus, the entire proximal margin can be submitted for evaluation as a donut in one block.

In a distal gastrectomy, the proximal margin can be wide, and the specimen should be opened first to examine the location of the tumor and its relationship to the resection margins. The decision as to where to take the frozen section is at the discretion of the pathologist based upon his/her judgment upon examination of the gross specimen. In the presence of a discrete lesion and gross margin clearance of more than 2 cm, a representative en face section at the site of the closest margin is adequate after the entire proximal margin is inked (Figure 20-8A). The remaining proximal margin is submitted for permanent evaluation. If the tumor is present within 2 cm from the margin, a representative perpendicular section closest to the tumor is recommended after the entire margin is appropriately inked (Figure 20-8B). When the tumor diffusely involves the stomach, particularly in cases of the diffuse subtype or in post neoadjuvant specimens in which the gastric

wall is fibrotic and the tumor bed is present as a diffuse scar, it is necessary to submit the entire proximal margin if this is surgically indicated. To facilitate the efficiency of this assessment, the entire proximal margin should be inked, carefully trimmed, rolled into a staked circle, and entirely submitted en face in two to three blocks (Figure 20-8C).

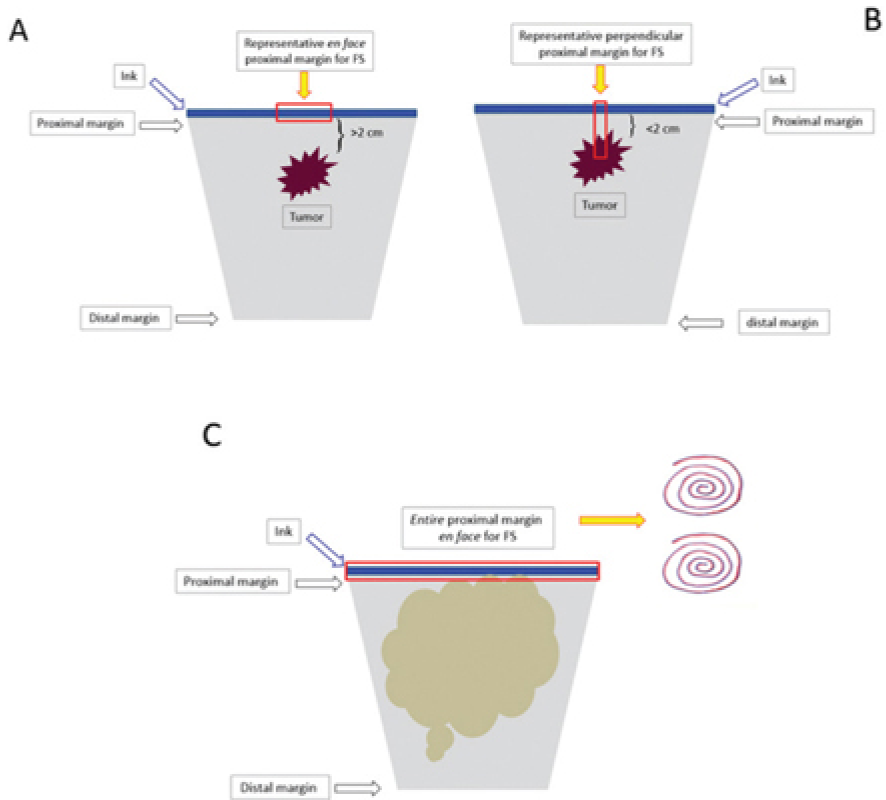

Figure 20-8. Intraoperative assessment of proximal gastric resection margin. A. A representative section of the proximal margin may be submitted for frozen section (FS) en face when the gross tumor clearance is >2 cm. B. A representative perpendicular section of the proximal margin may be submitted when the gross tumor clearance is <2 cm. C. If the entire proximal margin needs to be entirely submitted, it can be trimmed and submitted as stack rolls in two to three sections.

When the carcinoma is present on the mucosal surface, the margin status is grossly or microscopically evident. Oversight usually occurs when the cancer is present deep in the gastric wall as scattered malignant cells, particularly in cases of diffuse signet-ring cell subtype or status post neoadjuvant therapy (Figure 20-9). Therefore, an explicit knowledge of the specific subtype of gastric carcinoma in the preoperative biopsy and treatment status can facilitate an accurate evaluation of margin status at the time of intraoperative assessment.

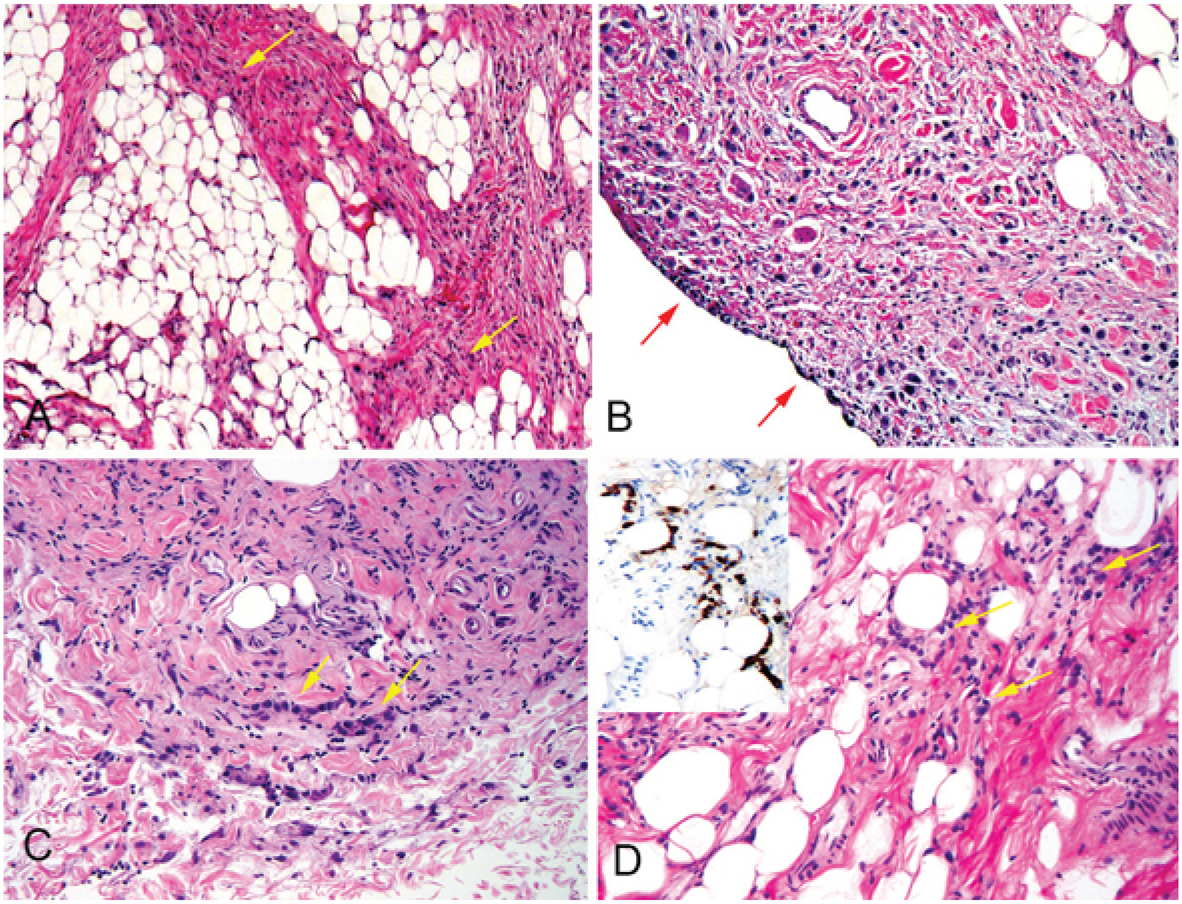

Figure 20-9. Challenging intraoperative assessment of gastric resection margin. A. The tumor cells infiltrate within fibrous septae in subserosal fat (arrows). B. The tumor cells are commonly present at the serosal surface (arrows). C, D. At intraoperative evaluation of the margin status, the tumor may be present in the deep gastric wall as scatted clusters or individual cells, which are better appreciated on an immunostain for cytokeratin.

For total gastrectomy performed for prophylaxis in the setting of *CDH1* germline mutations, both the proximal and the distal margins require intraoperative evaluation. The issue here is not about malignancy, but to assure that no gastric mucosa is left in the patient. Thus, the appropriate frozen section report should be "squamous mucosa present at the proximal margin and duodenal mucosa present at the distal resection margin, respectively."

V. Common pathologic findings

1. Histologic subtypes of gastric cancer

Gastric cancer represents a heterogeneous group of tumors with diverse pathogenesis, morphologic features, and molecular backgrounds. While recent genomic analysis has identified several subtypes of gastric adenocarcinoma by their genomic signatures,[4] histopathologic classification remains critical for clinical assessment of the disease and serves as the basis for the molecular classification of the disease.[20] Several systems have been proposed to aid in the classification of gastric adenocarcinoma based on the microscopic features of the tumor.[21] The two most commonly used histologic classifications are the Laurén classification (Figure 20-10) and the World Health Organization (WHO) systems,[22,23] with significant correlation between these two schemes.

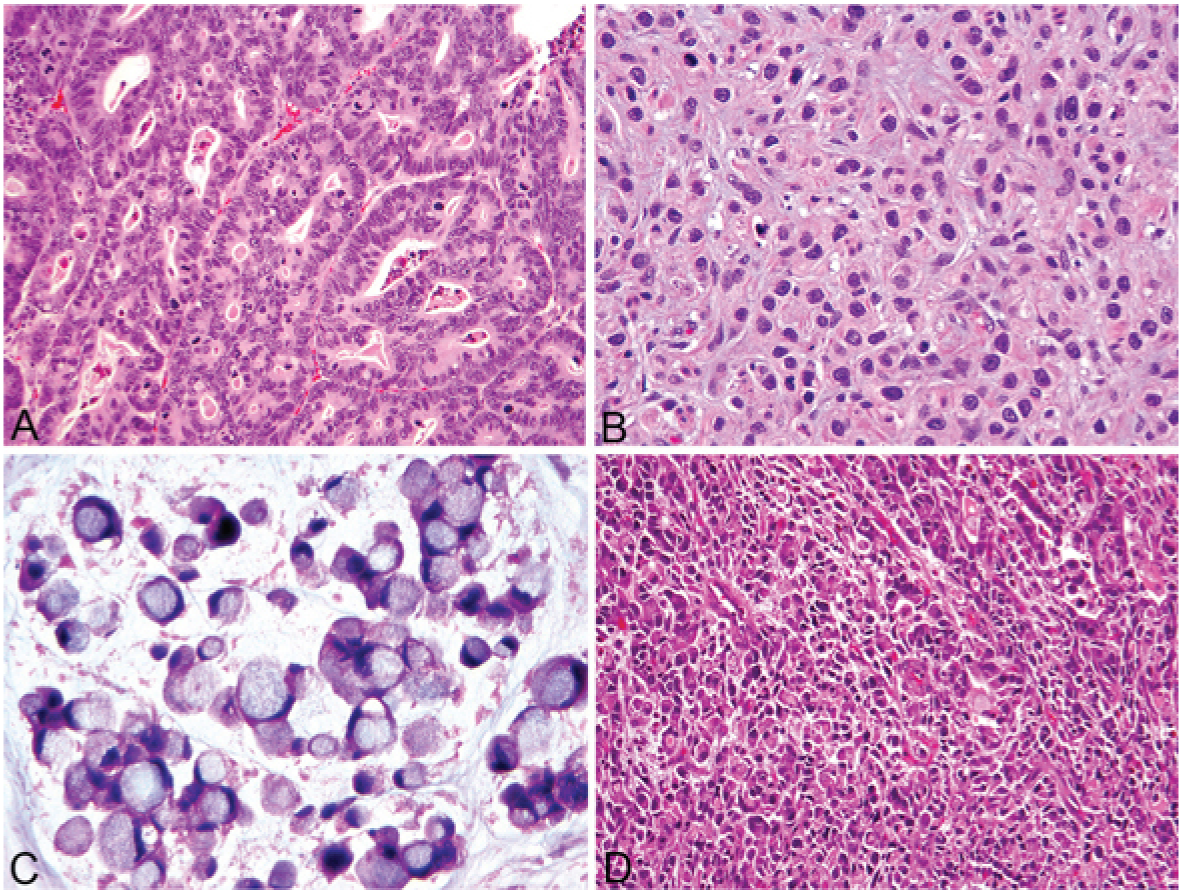

Figure 20-10. Lauren's histopathology classification of gastric cancer. A. Intestinal type adenocarcinoma with well-formed glandular and tubular architecture. B. Poorly differentiated diffuse type adenocarcinoma. C. Diffuse-type adenocarcinoma with intracellular mucin and signet ring cell features. D. Lauren's mixed type adenocarcinoma with a small component of poorly differentiated intestinal phenotype (upper right) and a poorly differentiated diffuse/poorly cohesive carcinoma with focal signet ring cell features (left).

Less-common variants of gastric carcinomas include the adenosquamous, hepatoid (Figure 20-11A), micropapillary, carcinoma with lymphoid stroma (medullary carcinoma) (Figure 20-11B), carcinoma with pancreatic acinar differentiation (Figure 20-11C), choriocarcinoma, fundic gland variant[24] (Figure 20-11D), undifferentiated subtypes, carcinoma with sarcomatous differentiation (Figure 20-11E), high-grade neuroendocrine carcinoma of small cell or large cell subtype (Figure 20-11F), and carcinoma arising in gastric heterotopia in the esophagus (gastric inlet) or pancreatic heterotopia.[25] The so called medullary carcinoma usually has an expansile growth pattern with intratumoral and peritumoral lymphocytic infiltration; this tumor phenotype is commonly associated with either Epstein-Barr virus (EBV) infection or microsatellite instability associated gastric carcinoma. When encountering these rare subtypes of gastric carcinoma, the relevant clinical implication is that a metastasis should be excluded before entertaining a diagnosis of primary gastric carcinoma in initial biopsies. In addition, any histologic subtype of gastric carcinoma, when poorly differentiated, can present with either partial or entirely sarcomatous features (sarcomatoid carcinoma) (Figure 20-13E), which is not uncommon in the upper gastrointestinal tract.

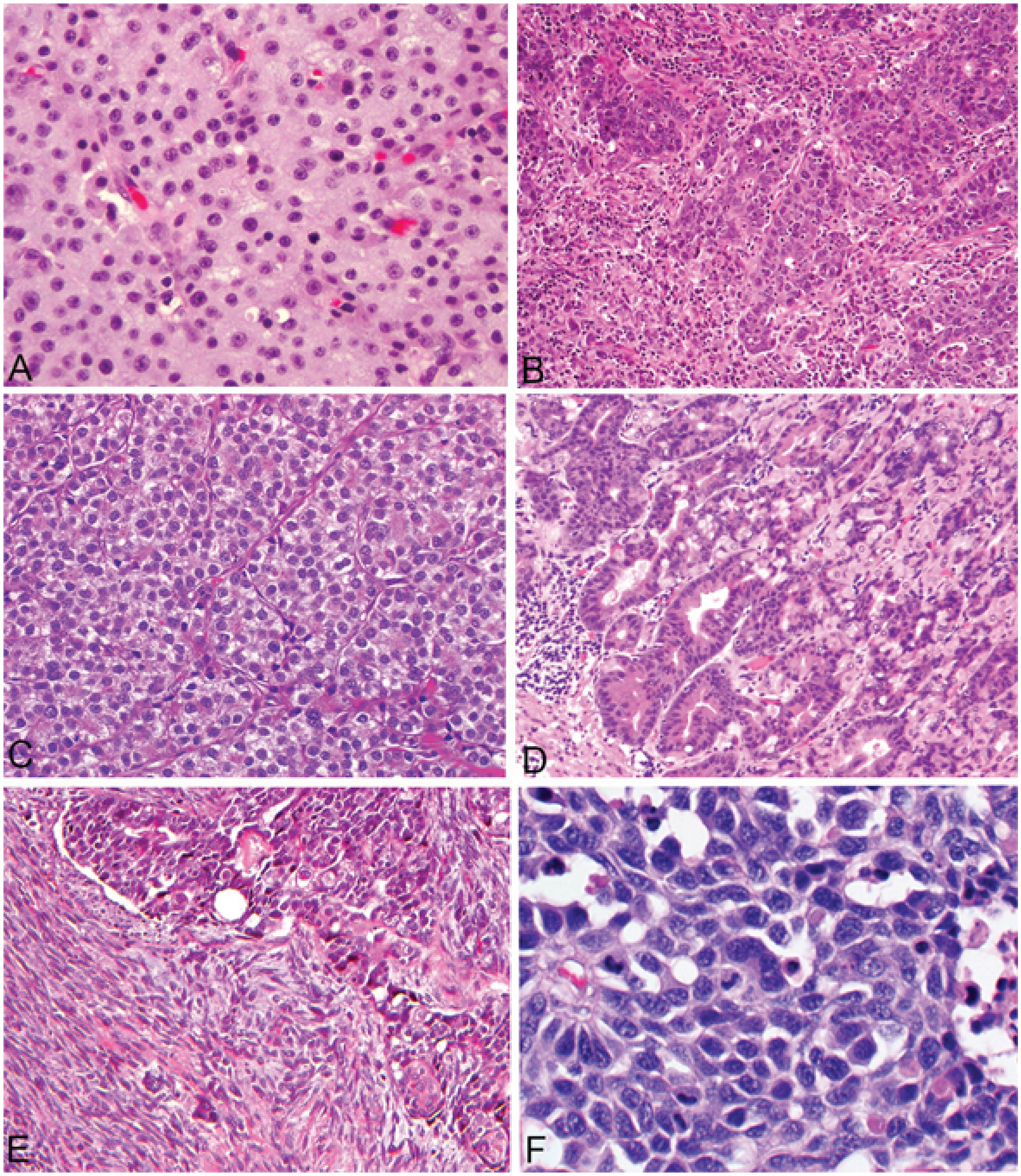

Figure 20-11. Uncommon variants of gastric carcinomas. A. Adenocarcinoma with hepatoid features. B. Medullary adenocarcinoma with markedly increased intraepithelial and stroma lymphocytes (small blue cells). C. Adenocarcinoma with prominent pancreatic acinar differentiation. D. Fundic gland adenocarcinoma. E. Undifferentiated carcinoma (upper right) with sarcomatous differentiated (low left). F. High-grade neuroendocrine carcinoma, small cell type.

2. Hereditary condition associated gastric neoplasms

Approximately 10% of all gastric cancers are familial.[26] Germline mutations in the E-cadherin *CDH1* gene account for 30% to 40 % of the rare syndrome known as hereditary diffuse gastric cancer (Figure 20-12A), and gastric cancers also occur less frequently as a component of other hereditary cancer syndromes. These include (1) Lynch syndrome with associated DNA mismatch repair gene deficiency (Figure 12B), (2) familial adenomatous polyposis (FAP) (Figure 20-12C), (3) gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) with mutation of APC-1B promoter region 27, (4) Li–Fraumeni syndrome with associated germline p53 mutation, (5) Peutz–Jeghers syndrome with associated *STK11* gene mutation (Figure 20-12D), (6) juvenile polyposis with associated *SMAD4, BMPR1A,* and *ENG* gene mutations.[26]

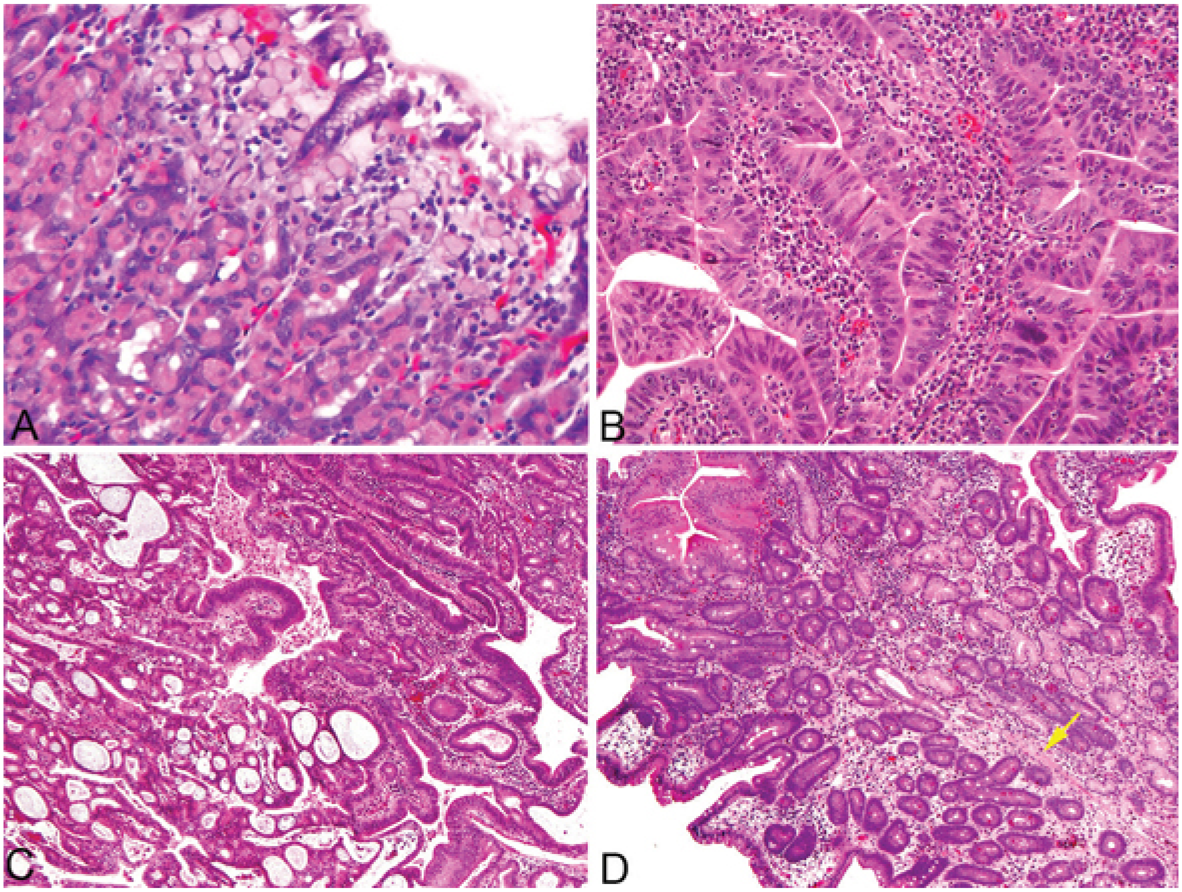

Figure 20-12. Hereditary condition-associated gastric neoplasms. A. Early hereditary diffuse gastric carcinoma with signet-ring cell morphology present in the superficial lamina propria. B. Heriditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome) associated intestinal type gastric adenocarcinoma exhibits increased intraepithelial and stromal lymphocytes. C. A familial adenomatous polyposis-associated adenocarcinoma (left) arising in a fundic gland polyp with dysplasia (upper right). D. Gastric Peutz–Jeghers polyp composed of irregular and architecturally distorted proliferation of foveolar glands with increased inflammation in the lamina propria and smooth muscle proliferation (arrow).

VI. Common potential staging pitfalls and solutions

1. Staging of early gastric adenocarcinoma

In contrast to colorectal adenocarcinoma, early stage gastric adenocarcinoma, even when confined to the mucosa, has a greater propensity for lymphovascular invasion. Thus, the staging system for early cancer of the stomach does not correspond with that of the colorectum. High-grade glandular dysplasia in the stomach is staged as carcinoma in situ (pTis),[28] whereas high-grade dysplasia in an adenoma is considered precancerous in the colorectum. Gastric adenocarcinoma with invasion into the lamina propria and muscularis mucosae is staged as pT1a; whereas in the colorectum it is staged as pTis, which may not require additional intervention if completely removed. To add more complexity to the matter, the interpretation of high-grade glandular dysplasia (pTis) and pT1a of gastric adenocarcinoma can be subjective, particularly in biopsies. Practically, both intramucosal (pTis) and superficially invasive (pT1a) gastric adenocarcinoma require surgical or endoscopic intervention; thus, the distinction between the two interpretations in a biopsy is less challenging for pathologists. However, the interpretation between low-grade and high-grade (pTis) glandular dysplasia would have clinical impact since the former is clinically observed and the latter necessitates prompt intervention. Thus, when dealing with an initial diagnosis of high-grade dysplasia in a gastric biopsy, it would be prudent to review the patient's clinical history and seek clinical/endoscopic consultation or a second opinion.

2. Site of tumor deposit and corresponding tumor stage

An isolated and irregular tumor deposit identified in fibroadipose tissue (excluding a lymph node replaced by tumor and a large vessel invasion by tumor) in a gastrectomy specimen or in lymphadenectomy specimens

could represent (1) a disjointed focus of carcinoma from the primary site by direct extension into the subserosa (pT3) or (2) an omental metastasis (pM1). The distinction between the two scenarios can be challenging on microscopic examination alone without the reference of its relation to the gastric wall. If the tumor deposit is identified grossly, it is important for the prosector who handles the specimen to document its exact location, which can facilitate the determination of its nature. In situations when the tumor deposit is only apparent microscopically, a discussion with the surgeon may be necessary to determine the extent of surgical resection and possible involvement of the omentum by carcinoma.

3. Adequate number of lymph nodes for staging

AJCC staging for gastric adenocarcinoma requires a minimum of 15 lymph nodes for adequacy. The number of lymph nodes removed appears to have prognostic implications.[29] Therefore, the effort for adequate lymph node retrieval should be emphasized during gross prosection and microscopic examination of the specimen. Inadequate number of lymph nodes may culminate in upstage (pN), ie, the missing lymph nodes would be considered as being positive; as a result, the patient may be subjected to unnecessary adjuvant chemotherapy. Therefore, repeat and thorough examination should be attempted when initial retrieval fails to achieve 15 nodes. If multiple attempts fail to identify more than 15 lymph nodes in the specimen, this should be documented as well for the record that the reported inadequate number of lymph node is not an oversight.

4. Evaluation of treatment response status post neoadjuvant therapy

Most patients with locally advanced gastric cancer in the Western countries receive neoadjuvant therapy. While the benefit of overall survival in this group of patients remains to be further evaluated, neoadjuvant chemotherapy could increase tumor resectability rate.[30] It is of note that there is a notable discordance between clinical/radiographic and pathologic assessment of treatment response.[31]

The assessment of pathologic response involves both the gross and the microscopic examination of the resected surgical specimen. The degree of treatment response for gastric adenocarcinoma is unpredictable and varies significantly from complete regression to minimal or inconspicuous response; thus, the knowledge of neoadjuvant status is important when examining a gastrectomy specimen. On gross examination, a complete or nearly complete response may present as a scar or unremarkable mucosa at the site of primary tumor; in the latter situation, re-review of the prior biopsy and its location are necessary for confirmation of the diagnosis and reference of the tumor bed. When encountering a profound gross treatment response, it is recommended that the entire tumor bed be submitted for histopathology evaluation for adequate staging.

At the microscopic level, a positive treatment-related effect is observed as abolition of the malignant epithelium and replacement by dense fibrosis, fibroinflammation, or acellular mucin pools. The pathologic response to treatment can be determined by the amount of residual viable carcinoma in relation to areas of fibrosis or fibroinflammation within the gross lesion. This relationship is expressed as the inverse percentage of a favorable treatment response.[31] Alternatively, a simplified three-tier grading system can be used as well.[32]

The presence of viable tumor cells suggests incomplete response. Viable tumor cells are defined by intact nuclear membrane, but not those with smudged cell borders and ragged nuclear membranes. Immunohistochemistry of cytokeratin is not recommended to determine the viability of tumor cells since dead/ghost epithelial cells also react to the antibody. Acellular mucin is regarded as a form of positive treatment response, not as viable tumor. The pathologic tumor stage of the residual carcinoma is based on the deepest focus of viable malignant epithelium of the gastric wall. Positive lymph nodes are defined as having at least one focus of viable tumor cells in lymph nodes.[31]

VII. Synoptic report

"Protocol for the Examination of Specimens From Patients With Carcinoma of the Stomach" from College of American Pathologists (CAP)[32] includes the most updated information from the AJCC staging system and WHO classifications.[23,28] The protocol can be used to generate final pathology report of gastric adenocarcinoma or as a resource to generate the required data elements for the synoptic reports, which includes:

- Organ(s) received
- Procedure performed

- Tumor site
- Tumor size
- Histologic subtype
- Histologic grade
- Depth of tumor extension
- Resection margin status
- Treatment effect (if applicable)
- Lymphovascular invasion
- AJCC pTNM (8th Edition)
- Additional pathologic findings
- Ancillary studies: HER2, DNA mismatch proteins, PD-L1, etc, as clinical indicated.3,4,33

Sample of Pathology Report of Gastric Adenocarcinoma

Distal stomach and proximal duodenum, partial gastrectomy:
Specimen Received: Portion of stomach
Procedure: Distal gastrectomy
Histologic Type: Residual adenocarcinoma exhibiting changes consistent with treatment effect
Treatment Effect: Present, involving 30% of the tumor
Lauren's Type: Intestinal
Histologic Grade: Moderately differentiated
Tumor Site: Antrum (lower third)
Tumor Size: length: 3.6 cm, width: 3.5 cm, maximal thickness: 1.2 cm
Microscopic Tumor Extension: Tumor penetrates serosa (visceral peritoneum)
Preexisting Polyp: Not identified
Lymph-Vascular Invasion: Present
Perineural Invasion: Present
Multicentricity: Not identified
Peritoneum (distant tumor deposit): Involved by tumor
Margins: All surgical margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: 2.6 cm
Specify margin: proximal resection margin
Additional Pathologic Findings: Intestinal metaplasia with focal low grade dysplasia
Lymph Nodes:
Number of lymph nodes with metastasis in this specimen: 2
Number of nodes examined in this specimen: 8
Number of nodes with metastasis in all specimens: 8
Number of nodes examined in all specimens: 38
TNM descriptors: y (posttreatment)
Primary Tumor (pT) (AJCC 8th Edition): pT4a: Tumor invades the serosa (visceral peritoneum)
Regional Lymph Nodes (pN): pN3: Metastasis in seven or more regional lymph nodes
Distant Metastasis (pM) (AJCC 8th Edition): M1 peritoneum
Ancillary studies:
Immunostain for HER2Neu is negative in tumor cells (Score 1+)
Results of immunohistochemical staining for DNA mismatch repair protein are as follows:
MLH1 Staining present in Tumor
MSH2 Staining present in Tumor
MSH6 Staining present in Tumor
PMS2 Staining present in Tumor
Conclusion: Tested DNA mismatch repair proteins by immunohistochemistry are retained in the tumor.

lmmunohistochemistry for PD-L1 expression (clone XX)
Combined Positive Score (CPS): 25/100
Relative contribution of tumor cells to the CPS: 80%
Relative contribution of inflammatory cells to the CPS: 20%

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21. Kidney

Sasan Setoodeh, MD; Ming Zhou, MD, PhD

Nephrectomy, either radical or partial, is performed to remove the entire (or a portion of the) kidney that contains tumor(s) or a nonfunctional end-stage kidney caused by systemic or chronic renal diseases. Pathologic examination of tumor-containing kidney specimens in adults is the focus of this review. Pediatric kidney tumors will be discussed in the pediatric pathology section. Such examinations provide not only accurate and clinically relevant diagnosis and classification, but they also yield information important for staging and prognosis prediction. The International Society of Urological Pathology (ISUP)[1] and the College of American Pathologists[2] have established practical guidelines for specimen processing.

I. Indication for nephrectomy

- Kidney cancers or tumors
- Nonfunctional kidneys caused by nonneoplastic diseases, such as medical kidney diseases, chronic infection, and polycystic kidney disease

II. What do we expect to see in the nephrectomy specimens?

A radical nephrectomy specimen consists of the entire kidney, including the collecting system and a variable length of ureter. The adrenal gland is usually removed en bloc with the kidney. The entire perirenal adipose tissue is removed to the level of Gerota fascia that encases the kidney in the perirenal fat. Variable lengths of the major renal vessels at the hilum are submitted. Regional lymphadenectomy is not generally performed, even with a radical nephrectomy. A few lymph nodes may occasionally be found in the renal hilum around major vessels. Other regional lymph nodes, including paracaval, paraaortic, and retroperitoneal, may be submitted separately.

A partial nephrectomy specimen may vary from a simple enucleation of the tumor to a portion of a kidney containing variable amount of renal parenchyma. The perirenal fat immediately overlying the resected portion of the kidney, but not Gerota fascia, is usually included.

III. Typical macroscopic appearance of kidney tumors

Renal tumors of different histologic types may have distinct gross appearance. Clear cell renal cell carcinoma is the most common renal cell carcinoma (RCC) subtype and accounts for 50% to 70% of renal tumors. They have a well-circumscribed border and a lobulated cut surface with golden yellow color (Figure 21-1A). Necrosis, hemorrhage, scar, and cystic changes are not uncommon, especially in large tumors. Fleshy or fibrous areas should raise a suspicion for sarcomatoid differentiation in an otherwise typical RCC (Figure 21-1B). Papillary RCC is the second most-common tumor and accounts for 15% to 20% of renal tumors. Most papillary RCCs are well circumscribed, containing foci of hemorrhage and necrosis. A surrounding fibrous pseudocapsule often is present (Figure 21-1C). Multifocality is more common in papillary RCC than in other types. Chromophobe RCC accounts for 5% to 10% of renal tumors, and they are often spherical, well-circumscribed, pseudo-encapsulated masses with homogeneous tan or light brown cut surfaces (Figure 21-1D). Central stellate scar may be seen in large tumors. Clear cell papillary RCC is usually small, circumscribed, and encapsulated. The cut surface is tan-white and yellow with grossly apparent fibrotic areas and ranges from completely solid to predominantly cystic (Figure 21-1E). Oncocytomas are typically solitary, well circumscribed, and nonencapsulated and have homogeneous cut surface with a characteristic mahogany-brown appearance (Figure 21-1F). A central zone of stroma is present in one third of the tumors. Papillary adenomas appear as well circumscribed although nonencapsulated, yellow-gray, cortical nodules. By definition, they are 15 mm or less in greatest dimension.

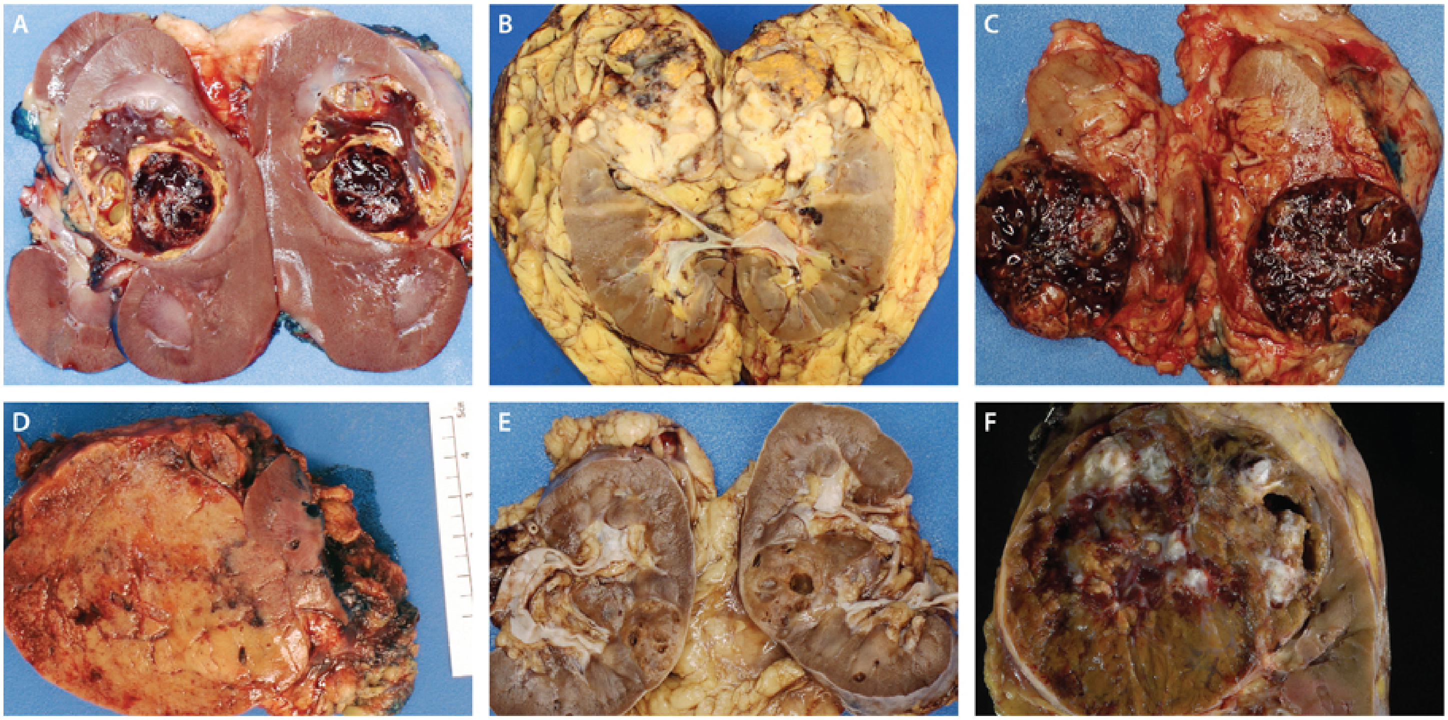

Figure 21-1. Gross morphology of common renal tumors. A. Clear cell renal cell carcinoma (RCC) has a well-circumscribed border and a lobulated cut surface with golden yellow color. Areas of hemorrhage, scar, and cystic changes are present. B. A clear cell RCC with large area of sarcomatoid differentiation that appears fleshy. C. Papillary RCC is well circumscribed and has a thick fibrous capsule and extensive hemorrhage and necrosis. D. A partial nephrectomy specimen contains a chromophobe RCC that is well circumscribed with homogeneous tan cut surface. E. A clear cell (tubule) papillary RCC is circumscribed and encapsulated. The cut surface is tan-white and predominantly cystic, with apparent fibrotic capsule and cystic septa. F. An oncocytoma is well circumscribed and partially encapsulated, and has homogeneous cut surface with a characteristic mahogany-brown appearance. A central stellate fibrotic scar is present.

IV. Dissection technique of nephrectomy specimens

Careful examination and documentation of the tumor extension beyond kidney into perinephric fat (pT3a), renal sinus (pT3a), Gerota fascia (pT4); presence of a tumor thrombus in the renal vein (pT3a) or its extension into the inferior vena cava (pT3b/c); and adrenal gland involvement (pT4 or M1, based on the continuity with the primary kidney tumor) provides important staging information.

Dissection technique of radical/total nephrectomy specimens

1. Review clinical and radiologic information.
- Grossers should review pertinent preoperative features, such as age of the patient, neoadjuvant treatment (tumor embolization and molecular target therapy), and imaging findings (number and size of tumors, and whether the tumor invades into any of the following structures: perinephric fat, sinus fat, collecting system, renal vein, and adrenal gland).
2. Review American Joint Committee on Cancer (AJCC) staging definitions for kidney cancers.
3. Orient the specimen.
- Use ureteral stump, which courses downward from the renal hilum, and adrenal gland, if present, to orient the specimen.
4. Record the weight and size of the entire specimen.
5. Ink the Gerota fascia/soft tissue margin in one color.
6. Shave margins from ureter, renal artery, and renal vein.
7. Bivalve the kidney.
- Insert a probe into the ureter or renal vein or both as a guiding plane to bivalve the kidney.
- Bivalve from the lateral aspect may be done but is not preferred.

8. Carefully examine the bivalve specimen and focus on the renal sinus to look for vascular vein invasion.
9. Photograph the specimen and the tumor.
10. Serially section the specimen.
11. Describe and record the tumor macroscopy, including focality, site, size in three dimensions, and extent of the tumor.

- Cut surface: circumscription, encapsulation, color, consistency, cystic change, necrosis, hemorrhage, calcification.
  - Percent of necrosis should be recorded.
- Extension of tumor
  - Limited to kidney
  - Extends beyond renal capsule into perinephric tissue
  - Extends into renal sinus
  - Extends beyond Gerota fascia
  - Extends into major veins (renal vein or inferior vena cava)
  - Extends into pelvicalyceal system
  - Extends directly (contiguous extension) into adrenal gland or other organs
- Distance from margins

12. Obtain fresh tissue for molecular or cytogenetic studies, particularly in younger patients.

- Make air-dried touch imprints for possible fluorescence in situ hybridization (FISH) studies.

13. Obtain fresh tissue for research, on the basis of institutional guidelines.
14. Describe the uninvolved renal parenchyma.

- Presence of other findings: cysts, calculi
- Color, thickness of cortex, distinction of corticomedullary junction, shape of papillae

15. Fix the specimen overnight using 10% neutral-buffered formalin.
16. Submit representative sections for light microscopy (Figure 21-3).

- At least one section per centimeter of tumor to include:
  - Tumor and the uninvolved kidney junction
  - Tumor and the perinephric adipose tissue
  - Tumor and the closest inked soft tissue margin
  - Tumor extension into the renal sinus (one section suffices if renal sinus invasion is grossly present or absent. Submit more sections if uncertain about invasion)
  - Tumor extension into the renal vein
  - Tumor areas with different gross appearance, particularly if white or fleshy smooth cut surface is present and suspicious for sarcomatoid change)
- Uninvolved kidney
  - A judgment about whether the amount of nonneoplastic renal parenchyma is sufficient for evaluation of medical kidney diseases should be made on a case-by-case basis.
  - In most cases, at least 5-mm-thick renal parenchyma is needed.

17. Palpate and submit all the hilar and the perirenal lymph nodes.
18. Describe the adrenal gland, if present.

- Size, color, nodularity
- If a tumor nodule is present, specify if it is contiguous with or separate from the primary kidney tumor.
- Submit sections from the involved (preferably showing interface) and the uninvolved adrenal gland.

Example of gross description of radical nephrectomy specimen

Received fresh and designated: Kidney, left

Procedure: Radical nephrectomy

Weight: 194 grams

Dimensions

Entire specimen: 19.5 x 15.3 x 14.1 cm

Kidney: 14.0 x 12.1 x 8.6 cm

Ureter: 6.2 cm in length, 0.4 cm in diameter

Renal vein: 1.1 cm in length, 0.9 cm in diameter

Renal artery: 1.2 cm in length, 0.3 cm in diameter

Ink code: Black

Tumor description

Site: Upper pole cortex (main tumor), lower pole cortex (nodule #2). Tumor protrudes into renal vein but is not attached to the vessel wall.

Size: 8.6 x 5.7 x 5.5 cm (main tumor), 1.8 x 1.2 x 0.5 cm (nodule #2)

Focality: Multifocal (2)

Circumscription: Well circumscribed

Cut surface: Encapsulated, solid, variegated golden yellow with multifocal necrosis and hemorrhage

Necrosis: 20%

Macroscopic extent of tumor: tumor extends into renal sinus, but does not extend into renal pelvis and to Gerota fascia

Margin status: All uninvolved

Tumor is 6.0 cm from ureter margin, 2.4 cm from renal vein margin, 2.1 cm from renal artery margin, and 0.8 cm from closest, black-inked, perinephric fat surgical margin.

Other lesions: Single, multilocular, thin-walled cyst with flat inner surface and no solid component, containing clear fluid in lower pole, 1.2 cm.

Uninvolved kidney: Cortical thickness is 0.8 cm, corticomedullary junction is well-defined.

Adrenal gland: 3.6 x 1.4 x 0.6 cm. A discrete, separate, tan-yellow 0.5 x 0.4 x 0.3 cm nodule is present in adrenal cortex. It is not contiguous with the renal tumor.

Hilar lymph nodes: Three lymph nodes ranging from 0.5 cm to 1.1 cm, uninvolved by tumor.

Section key

A1: Ureter, renal artery, and renal vein margins, en face

A2: Tumor and uninvolved kidney junction

A3: Tumor with perinephric adipose tissue

A4: Tumor with closest inked soft tissue margin, perpendicular section

A5-8: Tumor with renal sinus

A9: Tumor in renal vein

A10-A13: Tumor, representative sections

A14: Cyst wall, representative section

A15: Uninvolved renal parenchyma, representative section

A16: Adrenal gland, nodule with interface

A17-A19: Lymph nodes, entirely submitted

Dissection technique of partial nephrectomy specimens

Grossing a partial nephrectomy is similar to grossing a radical nephrectomy specimen; however, a few notable differences deserve mentioning. A partial nephrectomy usually does not have an attached ureteral stump to aid specimen orientation. It is critical to identify perinephric surface and parenchymal margin (Figure 21-2). Perinephric fat may be present but is often removed by the surgeon; therefore, the perinephric surface may not be a true surgical margin. Part of the parenchymal margin may be formed by a tumor capsule. In a partial nephrectomy specimen, these margins should be identified and inked with different colors.

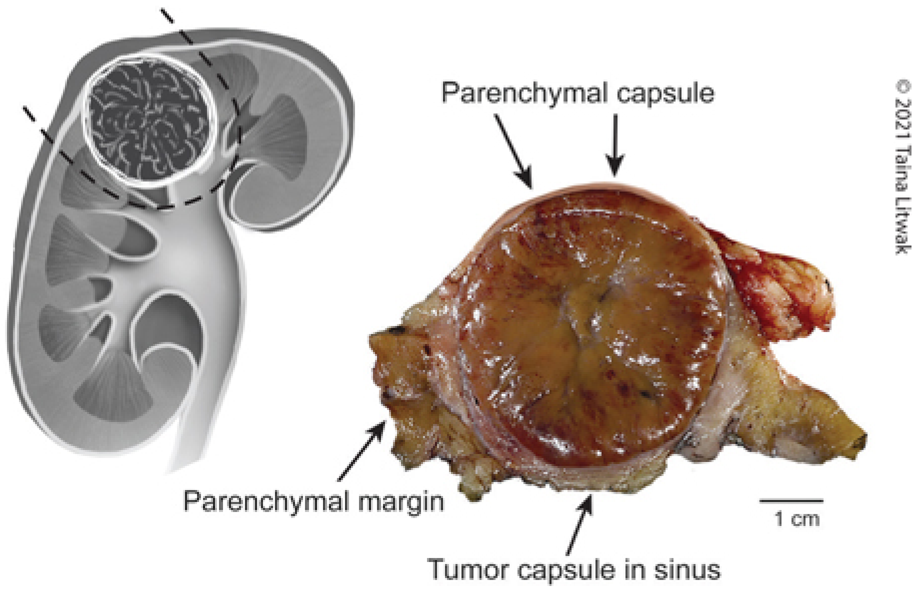

Figure 21-2. Grossing a partial nephrectomy specimen. It is critical to identify perinephric surface and parenchymal margin and ink them with different colors. Perinephric fat is often removed by the surgeon; therefore, it is not a true surgical margin. Part of the parenchymal margin may be formed by a tumor capsule.

V. Common pathologic findings in nephrectomy specimens

RCCs are the most common tumors in the kidney and are classified using the 2016 World Health Organization (WHO) classification system.[1,3] Other tumors, including mesenchymal, hematopoietic, and metastatic, are rare. Rarely, nonneoplastic lesions, such as xanthogranulomatous pyelonephritis, can mimic tumors.

VI. Common potential staging pitfalls and solutions

The AJCC TNM system is the well-accepted system to document the anatomic extent of the tumor in the specimens. T and N categories are derived from examining the resection and lymphadenectomy specimens; M category is assigned on the basis of clinical and pathologic examinations. The AJCC TNM staging should guide the gross examination and tissue sampling of nephrectomy specimens for histologic assessment.[3-5]

For staging purposes, tumor size at pathologic examination is required. For a tumor limited to the kidney, it is staged as T1 or T2, which is further divided into T1a (size ≤4 cm in greatest dimension), T1b (size >4 cm but ≤7 cm) or T2 (size >7 cm). To measure tumor with extrarenal invasion, the greatest dimension of the tumor mass should include the extrarenal extension. However, for tumor with intravascular extension, the tumor thrombus is excluded from the tumor size measurement.[4,5] If a specimen contains multiple tumor nodules, a maximum of five nodules should be measured, provided all tumors have similar gross appearance, and the largest is used to assign T category with prefix ”m” to indicate multiple tumors. Measurements should be taken for additional nodules if they have variable gross appearance. Tumors with differing histologies should have separate AJCC staging.

The renal sinus is an anatomical compartment separating the renal parenchyma from the upper collecting system (renal pelvis and calyces) and contains abundant adipose tissue, lymphatics, and thin-walled veins. It is an important route for extrarenal spread of RCC; therefore, it should be carefully assessed and generously sampled in order to detect renal sinus fat and vessel involvement. Clear cell RCCs that are greater than or equal to 7 cm show renal sinus invasion in more than 90% of cases. Any rounded nodules in renal sinus probably represent vascular invasion and should be sampled.

When the tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia, it is staged as pT3, which is further staged as T3a (tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not

beyond Gerota fascia), T3b (tumor extends into the vena cava below the diaphragm), or T3c (tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava).

If a tumor thrombus is present in the renal vein, it is important to determine if the renal vein margin is positive. The vascular margin is shaved. The margin is positive only when the tumor thrombus is present in the margin section and is adherent to the vascular wall.

Sarcomatoid differentiation represents a high-grade component in RCC and may have a firm or fleshy appearance that is different from the main tumor (Figure 21-3). Therefore, areas with different gross appearance in the same tumor should be generously sampled.

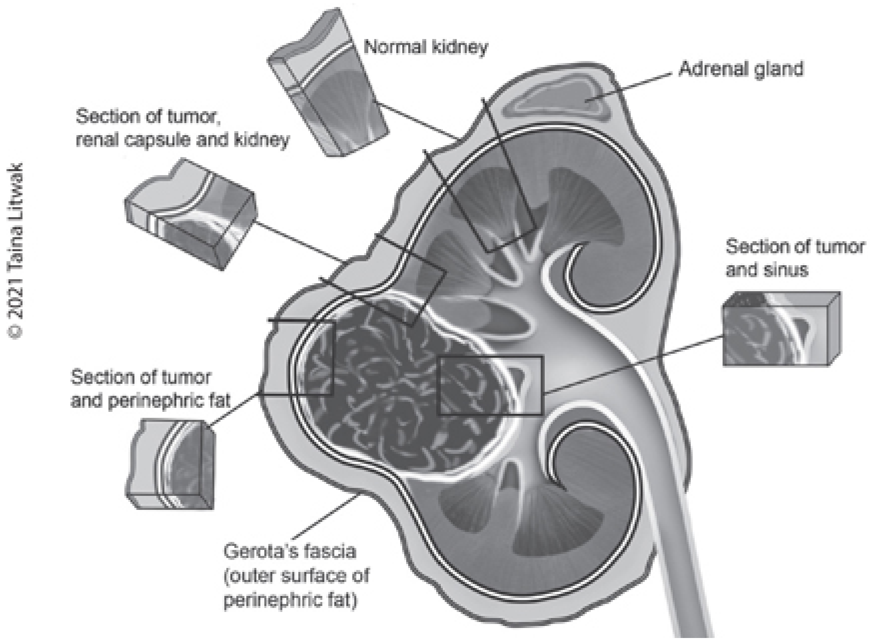

Figure 21-3. Schematic diagram for tissue sampling of a tumor-containing nephrectomy specimen. Sections should be taken to demonstrate the important anatomic relationship between the tumor and its surrounding structures, including renal capsule and peripheric fat, and renal sinus. Additional sections include tumor areas with different gross appearances, adrenal gland and normal kidney parenchyma.

Coagulative necrosis, confirmed on microscopic examination, correlates with adverse prognosis. On gross examination, the presence of tumor necrosis should be documented and estimated. At least one section of gross necrosis should be submitted for microscopic examination.

When renal carcinoma involves adrenal gland, it is important to document whether the involvement is contiguous with or separate from the primary renal tumor, the latter representing metastatic disease (pM1).

Hilar lymph nodes, when enlarged on imaging and grossly, are often submitted separately by surgeons. Grossers should palpate for and submit grossly identified nodes. Submission of fat to search for microscopic lymph nodes is nonproductive.

VII. What to include in the pathology report

The final pathology report should include critical information for staging and management, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, histologic type, the presence of sarcomatoid or rhabdoid features, WHO/ISUP histologic grade, tumor necrosis, tumor extension, margins status, nodal involvement, pathologic staging, and pathologic findings in nonneoplastic kidney. The presence of lymphovascular invasion and any additional pathologic findings may also be incorporated into the report.

Standard pathology report

Final diagnosis:

Kidney and adrenal gland, left, radical nephrectomy

- Clear cell RCC, 8.6 cm, WHO/ISUP nuclear grade 3, pT3aN0
- Tumor extends into renal sinus fat
- No lymphovascular invasion identified
- All ureteral, renal vascular, and soft tissue resection margins negative for tumor
- Three benign hilar lymph nodes negative for metastatic tumor (0/3)
- Single adrenal cortical nodule, 0.5 cm, negative for RCC

Synoptic report

Procedure: Radical nephrectomy

Specimen laterality: Left

Tumor site: Upper pole, lower pole

Tumor size: Greatest dimension: 8.6 cm; additional dimensions: 5.7 x 5.5 cm

Tumor focality: Unifocal

Histologic type: Clear cell RCC

Sarcomatoid features: Not identified

Rhabdoid features: Not identified

Histologic grade (WHO/ISUP Grade): G2

Tumor necrosis: Present

Specify percentage of necrosis: 20%

Tumor extension: Tumor extension into renal sinus

Margins: Uninvolved by invasive carcinoma

Lymphovascular invasion (excluding renal vein and its segmental branches and inferior vena cava): Not identified

Regional lymph nodes:

Number of lymph nodes involved: 0

Number of lymph nodes examined: 3

Pathologic stage classification (pTNM, AJCC 8th edition):

Primary tumor (pT): pT3a

Regional lymph nodes (pN): pN0

Pathologic findings in nonneoplastic kidney: None identified

Additional pathologic findings: Adrenal benign cortical nodule

Comment: Blocks A8 and A9 may be used for future ancillary studies if needed.

References

1. Srigley JR, Delahunt B, Eble JN, et al. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. *Am J Surg Pathol.* 2013;37:1469-1489.
2. Srigley JR, Zhou M, Allan R, et al. Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of Renal Tubular Origin. College of American Pathologists. 2020. Available at www.cap.org/cancerprotocols. Accessed May 27, 2020.
3. Humphrey PA, Moch H, Reuter VE, Ulbright TM, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs.* 4th ed. Geneva, Switzerland: WHO Press; 2016:11-76.
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5. Trpkov K, Grignon DJ, Bonsib SM, et al. Handling and staging of renal cell carcinoma: the International Society of Urological Pathology Consensus (ISUP) Conference recommendations. *Am J Surg Pathol.* 2013;37:1505-1517.

22. Penis

Ming Zhou, MD, PhD

Cancer of the penis is uncommon in developed countries. The risk is higher in patients with exposure to human papillomavirus (HPV) and those with lichen sclerosus, patients with psoriasis exposed to ultraviolet therapy, and tobacco users. Urethral cancer can also involve the penile structures. Penectomy, either partial or total, and circumcision are performed to remove the cancerous tissue of the penis. The amount of penis removed depends on the extent of the cancer. Various international authorities, including the College of American Pathologists,[1,2] have established practical guidelines for specimen processing and reporting.

I. Indication for penectomy

- Cancer of the penis and penile urethra that involves penile structures. However, the handling and processing of penectomy for primary urethral cancer are discussed in the chapter on urethrectomy specimens.
- Nonneoplastic lesions such as Fournier gangrene can also be a reason for penectomy.

II. What do we expect to see in the penectomy specimens?

Depending on the extent of tumor, a specimen may be a circumcision of the foreskin, which is often oriented with sutures, or partial or total penectomy that includes various lengths of the penile shaft. Total penectomy specimen may also include scrotal skin and inguinal lymphadenectomy contents.

III. Typical macroscopic appearance of penile tumors

Depending on the growth pattern, a penile carcinoma may present as an exophytic and cauliflower-like appearance to a flat or slightly elevated and/or deeply ulcerated lesion (Figures 22-1 through 22-3).

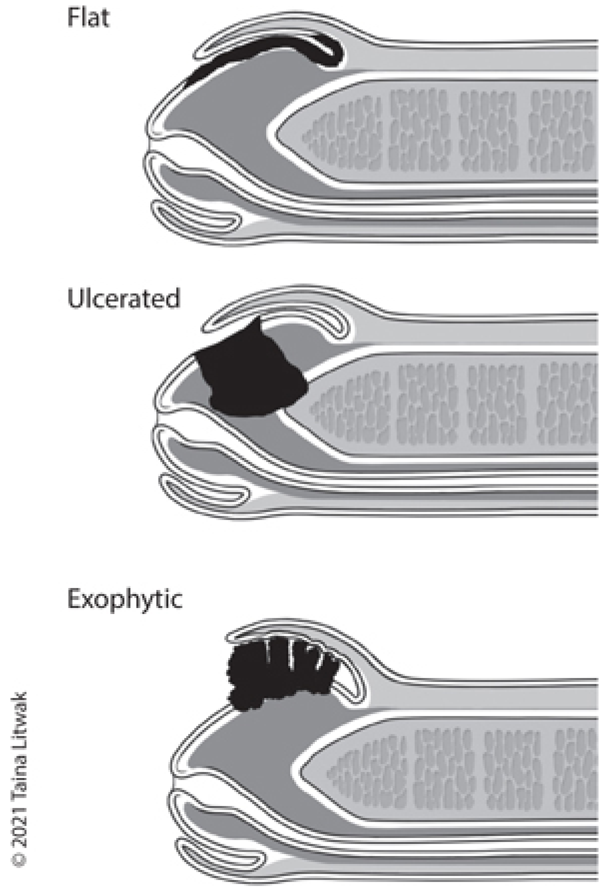

Figure 22-1. A diagram showing different gross growth patterns in penile cancers, including flat, ulcerated, and exophytic.

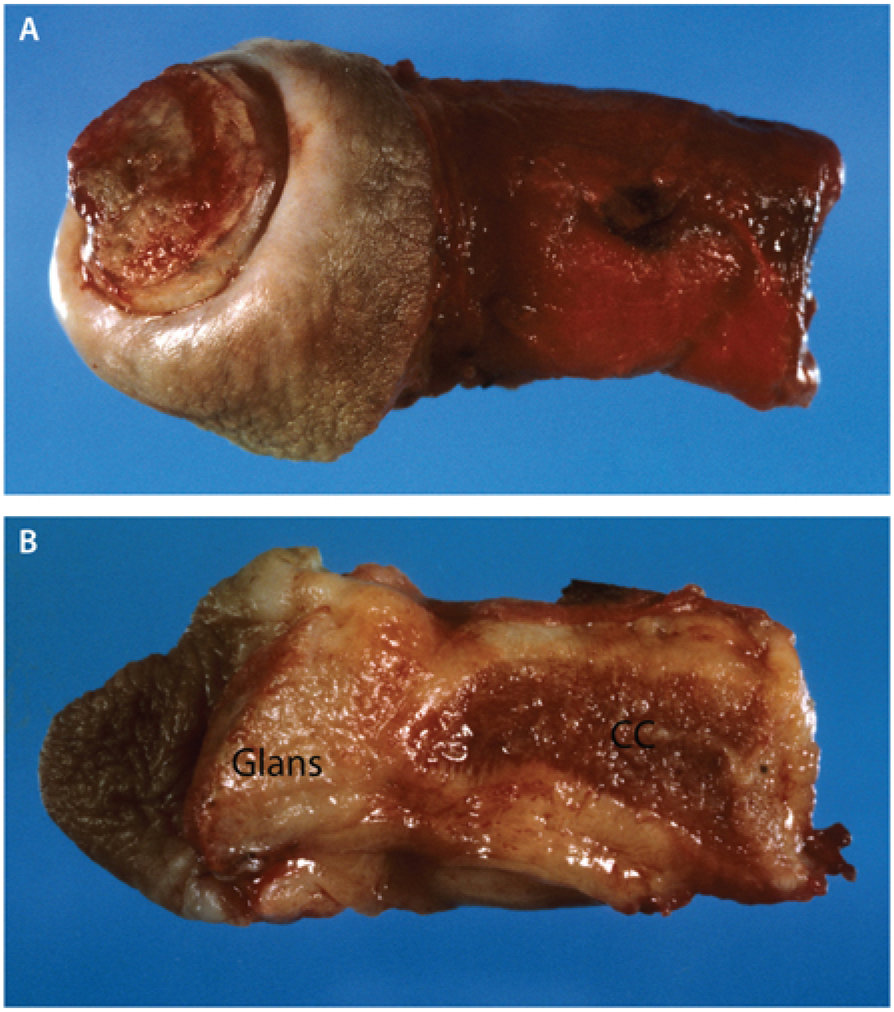

Figure 22-2. A partial penectomy specimen showing a slightly exophytic tumor involving the glans penis (A). Bisected specimen (B) shows the tumor involves the glans penis but spares the corpus cavernosum.

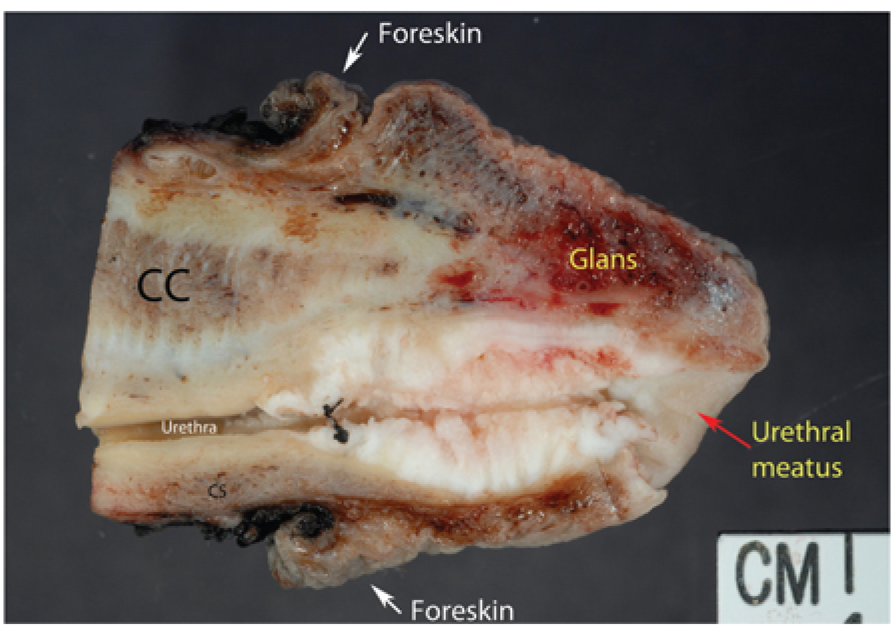

Figure 22-3. A bisected partial penectomy specimen reveals a tumor that arises in the distal penile urethra and invades the corpus spongiosum (CS). CC, corpus cavernosum.

IV. Dissection technique of penectomy specimens

Because cancers involving foreskin, glans, and shaft are staged differently,[1,2] it is critical to identify the anatomic structures that are primarily involved by the tumor. Gross dissection should also look for whether the tumor base is infiltrative or pushing and the depth of invasion, as these factors are prognostically important.

Dissection technique of circumcision and partial/total penectomy specimens

1. Review clinical and imaging information.
- Grossers should review pertinent preoperative clinical information and imaging findings. Because penectomy specimen may be markedly distorted by the tumor and/or surgical procedure, surgeon's impression of tumor location and imaging findings of involved penile structures and depth of invasion must be reviewed before grossing.
2. Review American Joint Committee on Cancer (AJCC) staging definitions for penile cancers.[2]
3. Orient the specimen.
- For circumcision specimens, surgeons may orient the specimen with sutures.
- For penectomy specimens, use available anatomic landmarks, including foreskin and coronal sulcus, glans, penile urethra, corpus spongiosum, and corpora cavernosa to orient the specimen (Figure 22-4).

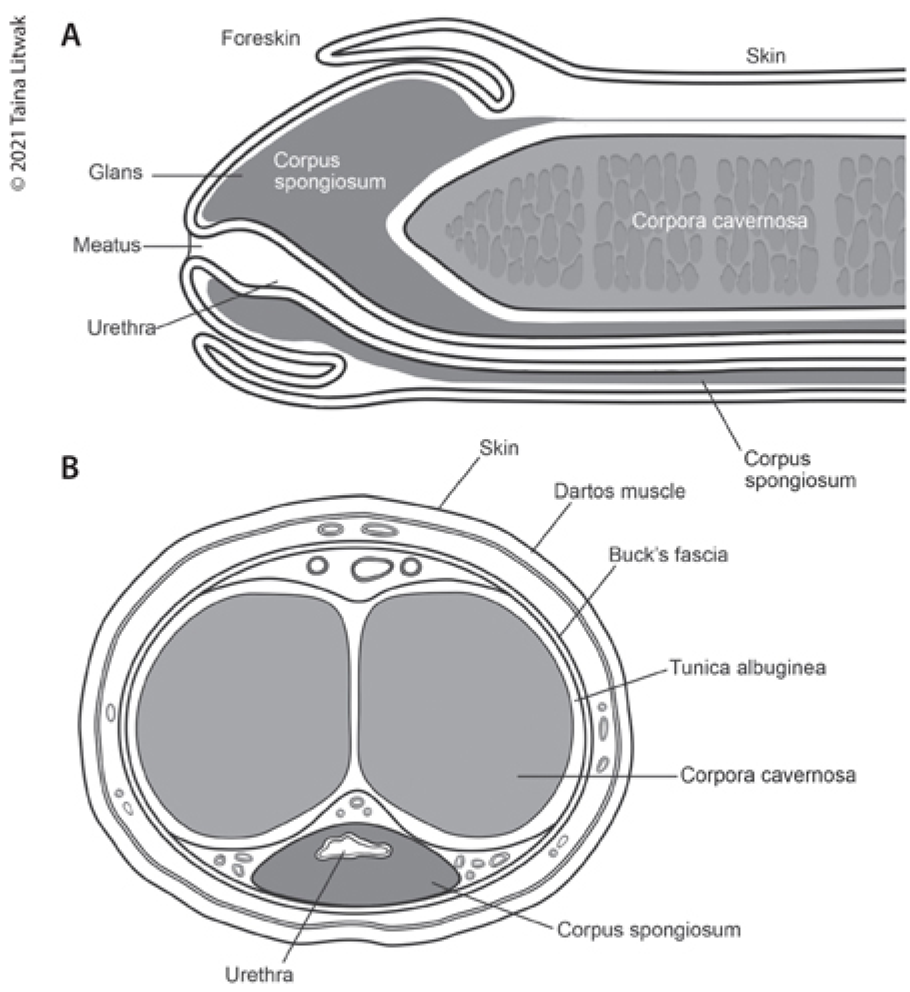

Figure 22-4. Longitudinal (A) and cross-section (B) of penectomy specimen showing penile structures. CC: corpus cavernosum; CS: corpus spongiosum.

4. Record the weight and size of the entire specimen.
5. Ink the specimen.
- For circumcision specimen, identify and ink in different colors the mucosal (coronal sulcus) and skin resection margins.
- For penectomy specimen, identify and ink in different colors the penile skin and the corporal and urethral mucosa margins.

6. Photograph the specimen and the tumor.
7. Fixation
- Circumcision specimen: Lightly stretch and pin the specimen to a cardboard and fix for several hours.
- Penectomy: Fix overnight.

8. Margin submission
- Circumcision specimen: Skin and mucosal margins, inked in different colors, are submitted together with the main specimen.
- Penectomy specimen: Shave and submit skin (with underlying dartos and penile fascia), corporal, and urethral mucosal margins. The latter two margins may be shaved and submitted in one section.

9. Dissection
- Circumcision specimen: May be cut and submitted like a skin eclipse or a cervical cone labeled from 1 to 12, clockwise.
- Penectomy specimen: If present, classify the foreskin as short, medium, long, and/or phimotic. Open the specimen longitudinally using the meatus and the urethra as the reference points. Do not probe the urethra. Divide the specimen into right and left halves. The urethra should be carefully examined for tumor involvement. Cross-section each half at 1-cm intervals. If the tumor is large and involves multiples structures (glans, sulcus, and foreskin), it is important not to remove the foreskin and to leave the entire specimen intact for sectioning.

10. Describe and record tumor macroscopy, including focality, site, size in three dimensions, and extent of the tumor.
- Appearance: Flat, exophytic (polypoid, papillary, verruciform, etc), ulcerated, pigmented
- Thickness of tumor
- Extension of tumor
  - Base of the tumor: pushing versus infiltrative
  - Maximum depth of invasion, measured from the epithelial-stromal junction of the adjacent nonneoplastic epithelium to the deepest point of invasion
  - Involvement of penile structures, including skin, urethra and meatus, corpus spongiosum, corpora cavernosa, tunica albuginea
- Distance from margins

11. Obtain fresh tissue for research on basis of institutional guidelines.
12. Cassette submission (Figure 22-5)

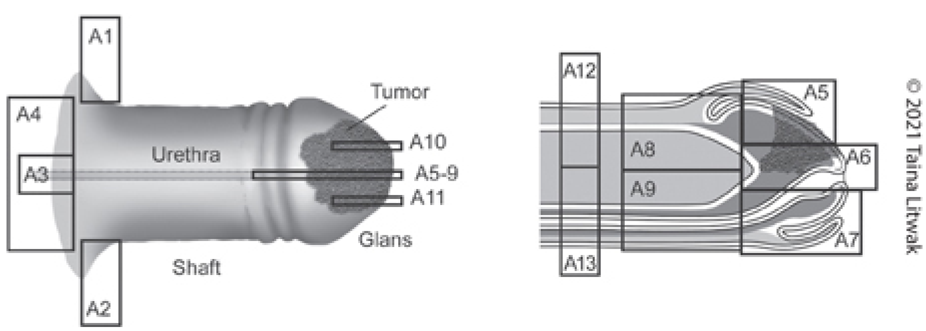

Figure 22-5. A diagram showing tissue sampling and cassette submission for a partial penectomy specimen. A1 and A2: penile skin margins; A3: penile urethral margin; A4: penile soft tissue margin; A5-11: tumor; A12 and 13: additional sampling of penile shaft.

- Circumcision specimen: Usually totally submitted.
- Penectomy: Resection margins should be completely submitted. The deepest invasion and involvement of penile structures must be sampled, including corpus spongiosum, corpora cavernosa, and urethra. For large

tumors, at least one section per centimeter tumor should be submitted and should include areas of different gross appearance. Grossly normal glans penis and other structures should also be sampled.

Example of gross description of penectomy specimen

Received fresh and designated: Partial penis

Procedure: Partial penectomy

Dimensions

Entire specimen: 6 x 3 x 2 cm

Glans penis: 3 x 2 x 2 cm

Shaft: 4 cm in length, 2 cm in diameter

Foreskin: Short (0.5 cm)

Penile skin: 1-2 cm in length

Ink code

Penile skin: black

Proximal shaft: green

Tumor description

Site: Glans penis

Size: 2 x 1.5 x 1.2 cm

Cut surface: Exophytic with ulcerated surface

Margin status: Uninvolved by tumor

Macroscopic extent of tumor: The tumor involves the corpus spongiosum of glans penis.

Description of uninvolved penis: The remainder of the glans penis/skin of shaft penis/penile foreskin are unremarkable. The corpora cavernosa/urethra are unremarkable.

Section key

A1-2: En face penile skin resection margin

A3: Urethral mucosal resection margin

A4: En face shaft resection margin

A5-A9: Longitudinal median section to include the tumor (see diagram)

A10-11: Additional sections of tumor

A12-13: Grossly normal corpus spongiosum and corpora cavernosa, complete cross-section

V. Common pathologic findings in penectomy specimens

The World Health Organization (WHO) classification of penile tumors was recently published.[3] Most penile cancers are squamous cell carcinomas (SCCs), and most arise from the epithelium of the distal portion of the penis (including glans, coronal sulcus, and mucosal surface of the prepuce). SCC of the usual type (keratinizing SCC) comprises about 50% to 60% of all cases. There are other SCC variants showing distinctive morphologic and outcome features. The different histologic subtypes correlate with different rates of regional/nodal and systemic dissemination. Penile cancer subtypes can be prognostically stratified in three groups. The low-risk group includes verruciform tumors such as verrucous, papillary, and warty/condylomatous carcinomas. More recently described subtypes, such as pseudohyperplastic and carcinoma cuniculatum of the penis, belong to this group. The high-risk category comprises basaloid, sarcomatoid, adenosquamous, and poorly differentiated SCC of the usual type. There is an intermediate category of metastatic risk that includes most SCCs of the usual type, some mixed neoplasms (such as hybrid verrucous carcinomas), and high-grade variants of warty/condylomatous carcinomas.

VI. Common potential staging pitfalls and solutions

AJCC staging should guide the gross examination of blocking of tissue samples for histologic assessment.[4]

Involved penile structures and the depth of invasion are two important anatomic factors that are important for staging and are determined by gross examination.

The vast majority of penile cancers arise from the mucosa that lines the glans penis and prepuce. Rarely, it arises from the penile skin. The tumor depth in small lesions is best obtained by perpendicularly sectioning along the tumor central axis. For large glans tumors, it is preferable to section the specimen longitudinally in half, with additional parallel sections of each half, using as an axis the central and ventral penile urethra. The depth of invasion is measured from the epithelial-stromal junction of the adjacent nonneoplastic epithelium to the deepest point of invasion. In larger tumors, especially verruciform ones, this method is, however, not applicable, and the tumor thickness and depth of invasion should be measured from the surface to the deepest point of invasion. Appropriate sections must be taken from areas of deepest invasion. Tumors invading different penile structures, including corpus cavernosa, corpus spongiosum, and urethra, are of different pathologic stages. Involvement of these structures should be grossly sought and sampled.

Category TX indicates that the primary tumor cannot be assessed, whereas T0 is used when there is no evidence of primary tumor. Tis and Ta denote carcinoma in situ (penile intraepithelial neoplasia [PeIN]) and localized noninvasive squamous cell carcinoma, respectively. T1 denotes tumors with subepithelial invasion—including laminal propria invasion in glans, dermis, lamina propria, or dartos fascia invasion in foreskin—and invasion into connective tissue between epidermis and corpora regardless of location in penile shaft. T1 is further divided into T1a (tumor without lymphovascular invasion or perineural invasion and is not high grade [grade 3 or sarcomatoid]) and T1b (tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade [grade 3 or sarcomatoid]). T2 tumor invades into corpus spongiosum (in glans or ventral shaft) with or without urethral invasion. T3 tumor invades into corpora cavernosa (including tunica albuginea) with or without urethral invasion. T4 tumor invades adjacent structures (ie, scrotum, prostate, pubic bone).

Positive margins adversely affect prognosis. Important margins to be examined in penectomy specimens include (1) proximal urethra and surrounding periurethral cylinder, consisting of epithelium, subepithelial connective tissue (lamina propria), corpus spongiosum, and penile fascia; (2) proximal shaft with corresponding corpora cavernosa, separated and surrounded by the tunica albuginea and Buck fascia; and (3) skin of shaft with underlying corporal dartos. The coronal sulcus (mucosal) margin and cutaneous margin should be entirely examined when evaluating circumcision specimens.

Lymph node staging depends on several anatomic and histologic factors. NX indicates that lymph node metastasis cannot be established. N0 denotes no lymph node metastasis. N1 denotes metastasis in two or fewer unilateral inguinal nodes without extranodal extension (ENE). N2 denotes metastasis in three or more unilateral inguinal or bilateral nodes. N3 denotes ENE of lymph node metastases or pelvic lymph node metastases.

As in other organ systems, there is no designation of MX or pM0. The absence of any clinical history or physical or radiologic findings suggestive of metastases is sufficient to assign the clinical M0 category (cM0). Metastasis confirmed on biopsy or other pathologic examination is assigned the pathologic M1 category. Patients with a negative biopsy of a suspected metastatic site are classified as clinical M0 (cM0).

VII. What to include in the pathology report

The final pathology report should include critical information for staging and management, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, histologic type and grade, location of tumor, size, tumor extent (deepest depth of invasion and penile structures involved by the tumor), lymphovascular invasion, perineural invasion, margins status, nodal involvement, pathologic staging, and any preneoplastic changes in the nontumor sites.

Standard pathology report

Final diagnosis

Penis, partial penectomy

- HPV-related papillary-basaloid squamous cell carcinoma, 1.5 cm, grade 3 (poorly differentiated)
- Tumor invades corpus spongiosum, with greatest depth of invasion of 10 mm

- Lymphovascular and perineural invasion identified
- HPV-related penile intraepithelial neoplasia, basaloid type, is present
- All resection margins negative for tumor
- Five inguinal lymph nodes negative for metastatic tumor (0/5)
- pT2N0 (see College of American Pathologists protocol)

Synoptic report

Procedure: Partial penectomy
Foreskin (presence and type): Present (uncircumcised); Short
Tumor site: Glans
Tumor size:
Greatest dimension (centimeters): 2 cm
Additional dimensions (centimeters): 1.5 x 1.2 cm
Tumor focality: Unifocal
Tumor macroscopic features: Ulcerated; Exophytic
Tumor deep borders: Infiltrative (jagged)
Histologic type: HPV-related SCC; Papillary-basaloid SCC
Histologic grade: G3: Poorly differentiated
Tumor extension: Carcinoma in situ; Tumor invades corpus spongiosum
Tumor thickness or depth of invasion: 10 mm
Margins: Uninvolved
Lymphovascular invasion: Present
Perineural invasion: Present
Regional lymph nodes:
Number of lymph nodes involved: 0
Number of lymph nodes examined: 5
Pathologic stage classification (pTNM, AJCC 8th edition):
Primary tumor (pT): pT2: Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
Regional lymph nodes (pN): pN0: No lymph node metastasis
Additional pathologic findings: HPV-related PeIN, basaloid type
Ancillary studies: Not performed
Comment: Blocks A5 and A6 may be used for future ancillary studies if needed.

References

1. Cubilla AL, Zhou M, Allan R, et al. Protocol for the Examination of Specimens From Patients With Carcinoma of the Penis. College of American Pathologists. 2017. www.cap.org/cancerprotocols. Accessed October 1, 2018.
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3. Humphrey PA, Moch H, Reuter VE, Ulbright TM, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs.* 4th ed. Geneva, Switzerland: WHO Press; 2016:11-76.

23. Prostate Gland

Sasan Setoodeh, MD; Ming Zhou, MD, PhD

Prostate resection specimens include transurethral resection and simple and radical prostatectomies. Other treatment modalities, such as cryosurgery and thermal and laser ablation, do not usually yield tissue.

I. Indications for prostate resection or prostatectomy

- Transurethral resection and simple suprapubic prostatectomy are for benign prostatic hyperplasia.
- Radical prostatectomy is for prostate cancer and other malignant tumors.

II. What do we expect to see in the prostate specimens?

Transurethral resection of the prostate (TURP) specimen consists of fragments of prostate tissue or chips. Simple prostatectomy specimen is enucleation of nodules of hyperplastic prostatic tissue and does not contain the entire prostate gland. No seminal vesicle or vas deferens is present in the specimen. Radical prostatectomy specimen consists of the entire prostate gland, seminal vesicles, and/or vasa deferentia, with bilateral regional/pelvic lymph nodes and fat. Periprostatic structures may be resected, including neurovascular bundles, adipose tissue, and fascia. Occasionally bladder neck or seminal vesicles may be spared in radical prostatectomy. Some specimens may include bladder or other adjacent pelvic organs resected with the prostate gland.

III. Typical macroscopic appearance of prostate tumors

Prostatic acinar adenocarcinoma is usually not grossly visible. It may, however, appear yellow, solid, and firm as compared with spongy, tan-white, benign prostatic parenchyma (Figure 23-1). Large and high-grade/stage tumor may be visible grossly, but clinically undetected T1c tumors are not grossly visible. Structural distortion, including asymmetry between the two sides of the gland and displacement of the fibromuscular band separating the transitional and peripheral zones ("surgical capsule"; Figure 23-1) may be a hint for presence of a tumor.

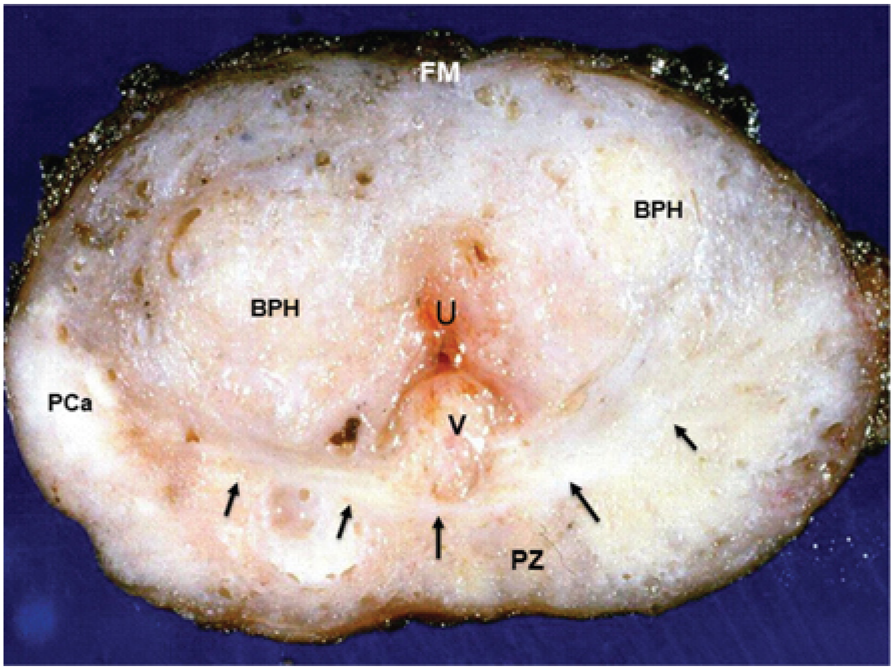

Figure 23-1. A slice of a radical prostatectomy specimen shows an ill-defined cancer (PCa) that appears yellow, solid, and firm, in contrast to the spongy, tan-white, benign prostatic parenchyma. Transition zones lateral to the urethra (U) ware expanded by benign prostatic hyperplasia (BPH). The anterior portion of the gland is fibromuscular layer (FM). Verumontanum (V) projects into the lumen from the posterior wall of the prostatic urethra (U). Arrows indicate "surgical capsule," a fibromuscular band that separates posterior peripheral zone (PZ) from the transition zones.

Adenocarcinoma of the prostate is often multifocal, 80% to 85% arising from the peripheral zone, 10% to 15% from the transitional zone, and 5% to 10% from the central zone. The anterior/transition zone tumors may be admixed with hyperplastic tissue and may not readily be recognized. Centrally located ductal adenocarcinoma may present as a friable polypoid or papillary mass protruding into the urethra. The rare stromal tumors, including stromal tumor of uncertain malignant potential (STUMP) and stromal sarcoma, may present as white-tan or gray solid or solid-cystic mass, often with smooth-walled cysts filled with bloody, mucinous, or clear fluid.

IV. Dissection technique of the prostate gland specimen Transurethral resection of the prostate (TURP)

Specimens comprise multiple tan and rubbery chips. The number of chips varies greatly from case to case. Measure the combined weight of the chips, and record their aggregate dimensions. The submission guideline is shown in Figure 23-2. For young men, submission of entire specimen may be considered to ensure detection of all T1a tumors.[1]

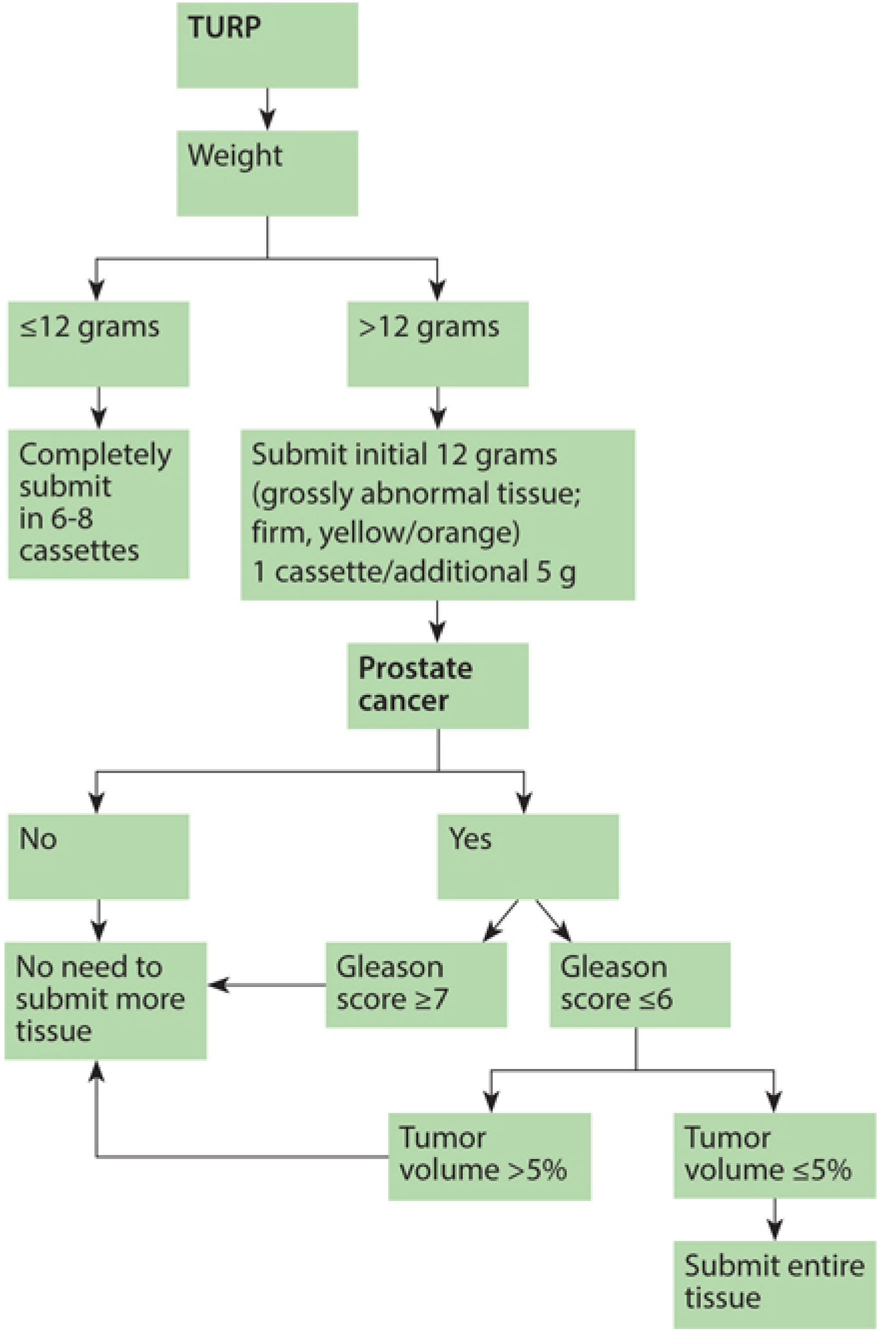

Figure 23-2. Tissue submission guideline for transurethral resection of the prostate (TURP) specimens.

Subtotal/simple/open prostatectomy (enucleation specimen)

Orientation of these specimens is usually not practical or possible. After weighing and measuring the tissue, serially section the specimen at 3-mm intervals. Note the appearance of the cut surface. Submit up to six to eight cassettes of tissue (three or four from each side) in absence of grossly suspicious lesions. Any grossly suspicious areas should be submitted.

Radical prostatectomy

1. Review clinical and radiologic information.

- Magnetic resonance imaging of the prostate is becoming increasingly sophisticated in detecting clinically significant prostate cancer as well as extraprostatic extension and seminal vesicle and bladder neck invasion. Preoperative imaging results and perioperative biopsy results may help grossers look for and sample tumor areas as well as extraprostatic extension that may not be evident grossly when partial tissue submission is used.

2. Orient the specimen.

• The prostate gland is shaped like an inverted cone. Orient the prostate by identifying the seminal vesicles and vasa deferentia, which insert into the posterior aspect of the base of the gland (Figure 23-3A).

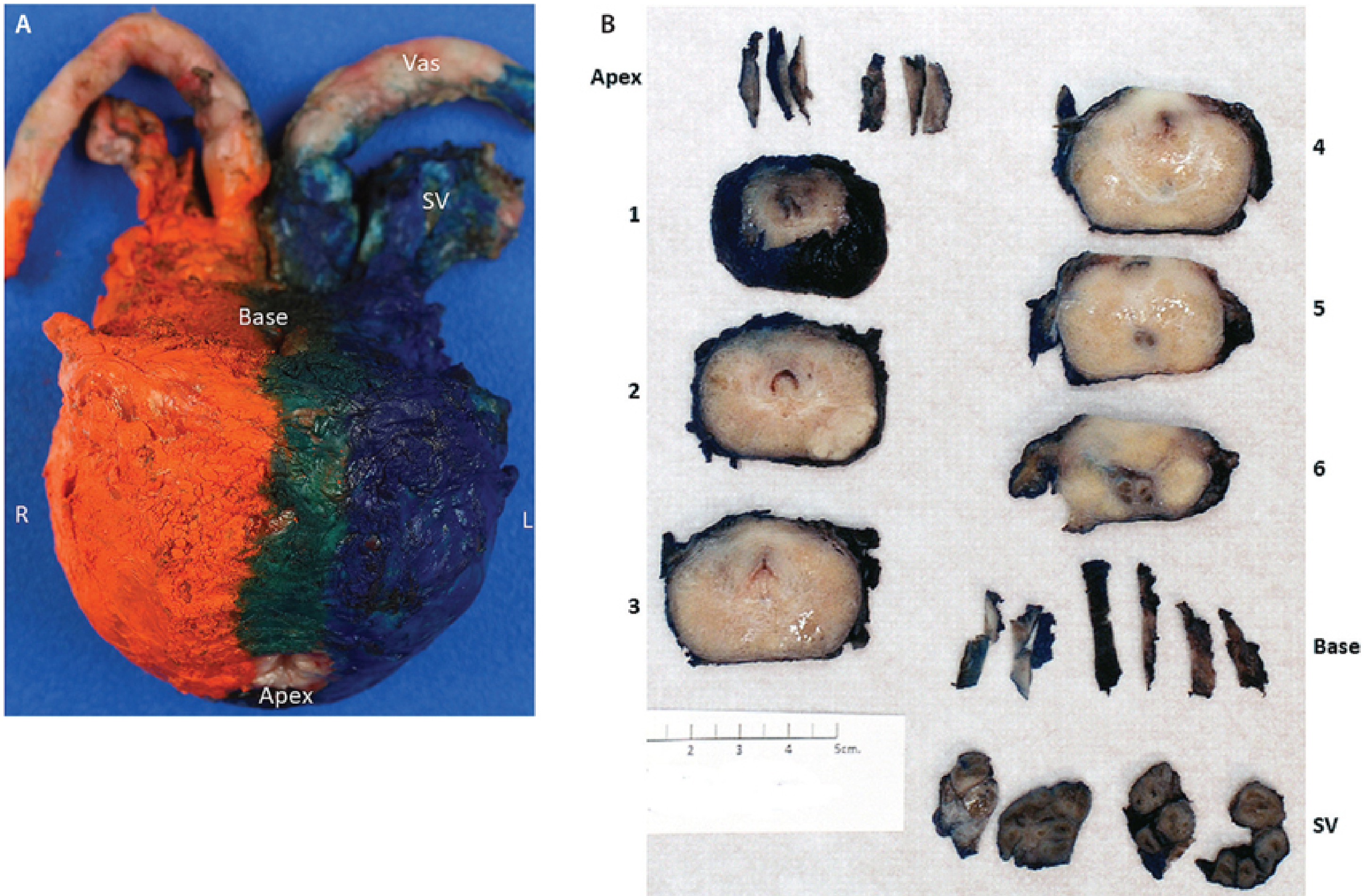

Figure 23-3. A. The prostate gland is shaped like an inverted cone. The seminal vesicles and vasa deferentia insert into the base of the gland posteriorly. It is inked with two colors, one for the right lobe and one for the left lobe. A strip of two different colors may be applied to and indicate the anterior and posterior surfaces. B. The gland is sliced at 3- to 5-mm thickness from apex to base. Apical and base slices are further sectioned parasagittally. Seminal vesicles are amputated at their junction with the prostate. The remaining slices can be submitted as whole mount or further divided and submitted routinely.

3. Record the weight and size of the prostate gland.
• Weigh the specimen both before and after the separation of the seminal vesicles.
• Measure the gland from base to apex (vertical), side to side (transverse), and anterior to posterior (sagittal).
4. Inspect the surface of the gland for possible induration or asymmetry.
5. Ink the outer surface of the prostate gland.
• Use at least two colors, one for the right lobe and one for the left lobe. A strip of two different colors may be applied to and indicate the anterior and posterior surfaces.
• A separate color can be used for possible surgical incisions or defects in the capsule of the prostate.
6. Obtain fresh tissue for research, based on institutional guidelines.
• Procure by scraping, shaving, or punching the cut surface, or by ex vivo needle biopsy of the areas that harbor cancer on imaging and biopsy studies.
• Ensure sampling methods do not compromise histopathologic examination of the prostatectomy.
7. Fix the specimen in 10% neutral-buffered formalin.
• Ideally, the prostate gland should be immersed in a volume of fixative 20 times the volume of the gland for at least overnight. Intragland injection of formalin may facilitate fixation—20 mL of formalin may be

injected deep into the gland at multiple sites using a 23-gauge needle.
- If the specimen is sliced before fixation for research tissue procurement, slices should be pinned to a flat surface to prevent tissue curling and retraction of the capsule.

8. Slice the entire prostate gland.
- Make a transverse section of the apex (coning the apex) and section it in vertical parasagittal plane (perpendicular sections).
- Similarly, make a transverse section of the base and slice it in vertical parasagittal plane.
- Serially slice the prostate from apex to base at 3- to 5-mm intervals in a transverse plane perpendicular to the posterior surface (Figure 23-3B).
  - Make sure slices have complete and continuous capsular margins.
  - The urethra follows a curved course through the gland and it should not be used as a point of reference for slicing.
- Amputate the seminal vesicles at their junction with the prostate. Slice each seminal vesicle and evaluate for metastatic nodules.

9. Describe tumor macroscopy and location.
- Prostate cancer is often grossly invisible; therefore, gross description of tumor macroscopy is of limited use.

10. Submit tissue for light microscopy.
- A radical prostatectomy specimen may be submitted in its entirety or partially sampled in a systematic fashion.
- Total submission of the prostate is ideal, but it may not be cost effective.
  - If the prostate gland is smaller than 30 g, it may be totally submitted.
- A variety of methods are available for partial submission and depend on whether the tumor is cT1c or cT2 disease and whether the cancer is grossly visible (Table 23-1).
- After partial submission, retain the remaining tissue slices in their original order and orientation in case additional sections are needed later.
- Look for and submit all regional lymph nodes.

Table 23-1. Protocol for Partial Submission of Radical Prostatectomy Specimens Based on Clinical Stage and Gross Findings

	cT1	cT2 with gross lesion	cT2 without gross lesion
Base of seminal vesicle	X	X	X
Base margin	X	X	X
Grossly suspicious lesion	X	X	
Section above apex	X	X	X
Apical margin	X	X	X
Alternate grossly normal slice	X		
Alternate grossly normal slice (posterior)			X

Section V. Example of gross description for radical prostatectomy specimen

Synoptic reporting format with free-texting option is preferred.

Transurethral resection

Received in formalin and designated: Prostate chips

Procedure: Transurethral resection/TURP
Number of fragments: Multiple
Weight: 9.6 g
Dimensions: 5.4 x 4.7 x 1.8 cm in aggregate
Section key
The specimen is entirely submitted in A1-A10.

Simple prostatectomy

Received in formalin and designated: Portion of prostate without seminal vesicles or vas deferens
Procedure: Simple prostatectomy/enucleation
Tissue procured for tissue banking: No
Weight: 48.6 g
Parenchyma: Nodular, yellow-tan
Dimensions: 5.2 x 4.6 x 4.5 cm in aggregate
Ink code
Orientation not provided. Inked black.
Number of slabs: 9 slabs
Section key
Representative sections submitted as follows:
A1-A4: One half of the specimen
A5-A8: The other half of the specimen

Radical prostatectomy

Specimen A: Received in formalin and designated: Prostate with attached bilateral seminal vesicles and vasa deferentia
Procedure: Robotic assisted laparoscopic radical prostatectomy
Weight: 32.5 g
Dimensions
- Entire specimen: 7.5 x 5.2 x 4.3 cm
- Prostate
  - 3.5 cm from apex to base
  - 3.9 cm from left to right
  - 3.1 cm from anterior to posterior
- Right seminal vesicles: 3.0 x 0.9 x 0.7 cm
- Left seminal vesicles: 2.2 x 0.6 x 0.5 cm
- Right vas deferens: 2.9 x 0.9 x 0.8 cm
- Left vas deferens: 1.8 x 0.5 x 0.5 cm

Ink code
Right side: orange
Left side: blue
Posterior mid-strip: black
Anterior mid-strip: green
Number of slabs: 6 slabs, from apex to base (including apex and base)
Cut surface: Nodular, yellow-tan
Tumor description (if grossly evident)
- Site: Right posterolateral aspect of slabs 1 to 4
- Cut surface: firm, yellow, homogenous
- Size: 2.1 cm (apex to base) x 1.2 cm (left to right) x 1.1 cm (anterior to posterior)
- Capsule: Focally disrupted at left anterolateral-mid and inked purple

Included in research protocol: No
Tissue procured for tissue banking: No

Section key

Entirely submitted as follows:

A1-2: Right apex, perpendicular sections, entirely submitted
A3-4: Left apex, perpendicular sections, entirely submitted
A5: Slab 2, right
A6: Slab 2, left
A7: Slab 3, right, anterior
A8: Slab 3, right, posterior
A9: Slab 3, left, anterior
A10: Slab 3, left, posterior
A11: Slab 4, right, anterior
A12: Slab 4, right, posterior
A13: Slab 4, left, anterior
A14: Slab 4, left, posterior
A15: Slab 5, right
A16: Slab 5, left
A13: Right base, perpendicular sections, entirely submitted
A14: Left base, perpendicular sections, entirely submitted
A15: Right seminal vesicle interface and vas deferens margin
A16: Left seminal vesicle interface and vas deferens margin

Specimen B: Received in formalin and designated: Right pelvic lymph nodes
Description: Two irregular fragments of fibrofatty tissue
Dimensions: 7.5 x 5.0 x 2.5 cm, in aggregate
Number and dimension of possible lymph nodes: 3; 0.9 cm greatest dimension
Other: A single firm nodule identified, 0.3 x 0.2 x 0.2 cm

Section key

B1: One lymph node, bisected
B2: Two lymph nodes, intact
B3: Firm nodule, entirely submitted

Specimen C: Received in formalin and designated: Left pelvic lymph nodes
Description: Two irregular fragments of fibrofatty tissue
Dimensions: 6.0 x 5.0 x 2.5 cm, in aggregate
Number and dimension of possible lymph nodes: 4; 1.0 cm greatest dimension
Other: A single firm nodule identified, 0.5 x 0.2 x 0.2 cm

Section key

C1: One lymph node, bisected
C2: Two lymph nodes, intact
C3: Firm nodule, entirely submitted

VI. Common pathologic findings in prostatectomy specimens

The most common invasive prostate cancer is acinar adenocarcinoma and its histologic variants (atrophic, pseudohyperplastic, etc) (WHO classification[2]). Ductal adenocarcinoma is often intermixed with high-grade and high-volume acinar carcinoma. Other carcinomas, including urothelial, squamous cell, basal cell, and neuroendocrine carcinomas, are rare. Metastatic bladder and colorectal carcinomas are rarely seen in prostatectomy specimens. Mesenchymal tumors, such as prostate stromal neoplasms, may also be encountered. High-grade prostatic intraepithelial neoplasia is frequently seen in the prostatectomy specimens. Intraductal carcinoma is sometimes present together with high-grade and high-volume acinar carcinoma. A variety of additional nonneoplastic conditions may be present in prostatectomy specimens, including benign prostatic hyperplasia and inflammation.

VII. Common potential staging pitfalls and solutions

Specimen handling, gross examination, and tissue blocking should be guided by the *AJCC Cancer Staging Manual,* 8th edition,[3] and recommendations from professional organizations.[4]

Prostate carcinoma (PCa) with extraprostatic extension or bladder neck invasion is staged as pT3a. Therefore, submitting the entire gland with attached fat, neurovascular bundles, fascia, or resected bladder neck is preferred for evaluation of extraprostatic extension and positive surgical margins. However, if a prostate specimen is large (>30 g), one may opt for partial tissue submission, the method of which is outlined in Table 23-1. For partial submission, grossers may use the imaging and biopsy results to help focus on the areas with cancer and extraprostatic extension.

Presence of seminal vesicle invasion (T3b) should be evaluated with a section of the junction of the base of the gland and the seminal vesicle for contiguous spread of tumor. This should be considered the minimum necessary to adequately sample the seminal vesicles. Remaining blocks to assess the rarer situation of noncontiguous spread could be taken if desired or if areas macroscopically suspicious for invasion are identified.

Both basal and apical margins should be inked, coned, and perpendicularly sectioned and submitted for microscopic evaluation. It is not recommended to shave and submit margins en face because it may result in false-positive margins.

Regional lymph nodes are those of the true pelvis located below the bifurcation of the common iliac arteries. In a small but significant number of cases, the metastatic implants are present in adipose tissues, not as grossly recognized lymph nodes. There is no consensus regarding the optimal method for sampling the lymph nodes. It is recommended to look carefully for and submit all macroscopic lymph nodes and suspicious firm areas in the adipose tissue from pelvic lymphadenectomy specimens. We do not advocate total submission of the lymphadenectomy tissue.

The use of whole-mount sections of radical prostatectomy specimens has the advantage of displaying the architecture of the prostate and the location of tumor nodules more clearly, and it is easier to compare the pathologic findings with those obtained from imaging studies. However, the whole-mount sectioning is more costly and technically more difficult to perform and has several other issues such as slide and block storage. It is therefore not routinely performed in histology laboratories.

VIII. What to include in the pathology report

The final pathology report should include information critical for staging, prognosis, and treatment decision making, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is preferred when available.

Information provided should include the procedure performed, histologic type, Gleason score and grade group, tumor volume quantification, and parameters that are required for staging, including extraprostatic extension, bladder neck and seminal vesicle invasion, surgical margins, and treatment effect. Other data that are optional to report include percentage of Gleason pattern 4/5, intraductal carcinoma, location, measurement and Gleason grade of cancer glands at the extraprostatic extension and positive surgical margins, microscopic lymphovascular invasion, size of largest positive lymph node and metastatic focus, extranodal extension, and additional pathologic findings.

Standard pathology report

Final pathologic diagnosis

A. Right pelvic lymph nodes, dissection

- Three lymph nodes negative for metastatic carcinoma (0/3)

B. Left pelvic lymph nodes, dissection

- Three lymph nodes negative for metastatic carcinoma (0/3)

C. Prostate, radical prostatectomy

- Adenocarcinoma of the prostate, Gleason score 4 + 5 = 9 (grade group 5)

- Extraprostatic extension identified
- No seminal vesicle invasion identified
- All surgical resection margins negative for carcinoma
- AJCC TNM stage: mpT3a N0

Synoptic report

Procedure: Radical prostatectomy
Prostate Size
Weight: 35 g
Size: 4.5 x 4.9 x 4.0 cm
Histologic type: Acinar adenocarcinoma
Histologic grade: Gleason pattern
 Primary Gleason pattern: 4
 Secondary Gleason pattern: 5
 Total Gleason score: 9
Grade group
 Grade group 5
Intraductal carcinoma
 Present
Tumor quantitation
 Estimated percentage of prostate involved by tumor: 60%
 Dominant nodule: Present
 Size: 27 x 20 x 14 mm
 Location: Right posterior
 Non-index nodule
 Size: 45 x 27 x 9 mm
 Location: Anterior midline extending bilaterally
 Gleason score of non-index nodule: 3+4=7
Extraprostatic extension: Present, nonfocal
Location: Right posterior mid
Urinary bladder neck invasion: Not identified
Seminal vesicle invasion: Not identified
Margins: Uninvolved by invasive carcinoma
Treatment effect: No treatment effect identified
Lymphovascular invasion: Not identified
Perineural invasion: Present
Regional lymph nodes
Number of lymph nodes involved: 0
Number of lymph nodes examined: 6
Pathologic stage classification (pTNM; AJCC, 8th edition)
 TNM descriptors: m (multiple)
 Primary tumor (pT): pT3a: Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
 Regional lymph nodes (pN): pN0: No positive regional nodes
Additional pathologic findings
 High-grade prostatic intraepithelial neoplasia
 Nodular prostatic hyperplasia
Ancillary studies: Not performed
Comments: Blocks that may be used for future ancillary/molecular studies, if needed: C3 and C4.

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24. Testis

Sasan Setoodeh, MD; Ming Zhou, MD, PhD

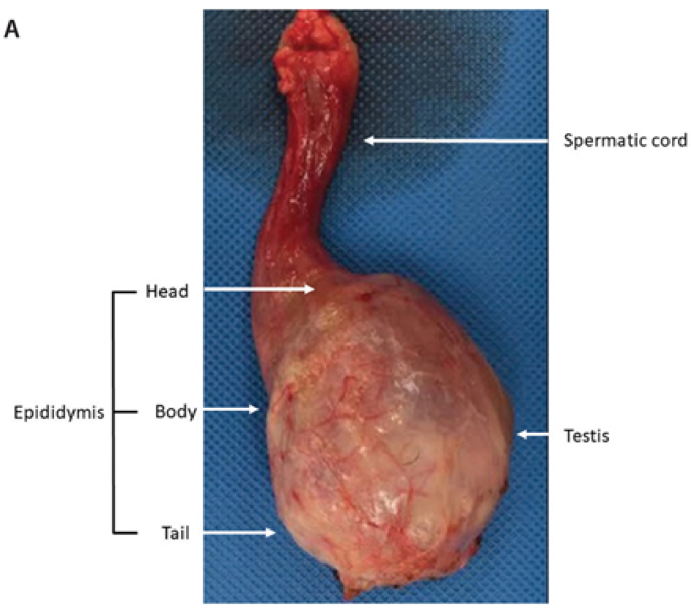
Orchiectomy is performed to remove tumors in the testis and paratesticular structures, including germ cell tumors (GCTs), sex cord–stromal tumors, other miscellaneous tumors, and paratesticular mesenchymal tumors. Retroperitoneal lymph nodes are considered regional lymph nodes for testicular cancers and may be removed by retroperitoneal lymphadenectomy. Subtotal or partial orchiectomy is rarely performed for benign testicular or paratesticular lesions. Handling of the orchiectomy specimens for postpubertal GCTs and malignant sex cord–stromal tumors of the testis is the focus of this review.

I. Indication for radical orchiectomy

Testicular and paratesticular tumors, the majority of which are GCTs.

II. What do we expect to see in the radical orchiectomy specimens?

A radical orchiectomy specimen consists of the testis, the surrounding tunica vaginalis, the epididymis, and the spermatic cord. It is usually enclosed in the spermatic fascia and cremaster muscle and may include the scrotal skin. The tunica vaginalis is a closed peritoneal sac partially surrounding the testis (Figure 24-1). The seminiferous tubules of the testis exit at the hilum/mediastinum into the rete testis and join the epididymis, which is in continuity with vas deferens in the spermatic cord. The hilum/mediastinum does not contain dense capsule of the tunica albuginea and is therefore a major route for local extension of the tumor.



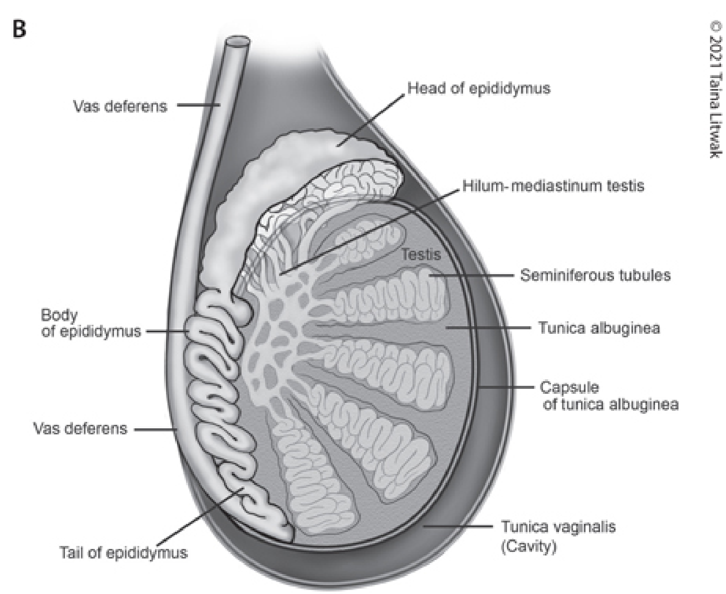


Figure 24-1. Anatomy of testis and paratestis. A. A radical orchiectomy is enclosed in spermatic fascia and cremaster muscle. The specimen can be oriented using the epididymis and spermatic cord as landmarks. B. After bivalving the specimen, the epididymis and distal spermatic cord and part of the testis are surrounded by tunica vaginalis, a potential space. The surface of the tunica albuginea must be inspected carefully for tumor involvement.

The visceral and parietal layers of tunica vaginalis do not normally adhere to each other except in the spermatic cord. Any adherence should raise the suspicion for tumor involvement.

III. Typical macroscopic appearance of testicular tumors

GCTs have variable gross appearances depending on their histologic types. It is very common that several histologic types are present in the same tumor. Seminomas, the most common GCT and accounting for about 50% of the cases, are usually well circumscribed, homogeneous, solid, often lobulated, with creamy tan or gray-

white color, soft and fleshy texture, and frequently bulging out of the surrounding parenchyma (Figure 24-2A). Hemorrhage and necrosis often indicate the presence of nonseminomatous component. Seminomas with interstitial growth may not be grossly evident. Embryonal carcinomas typically show a variegated cut surface that is solid tan-white with hemorrhage and necrosis (Figure 24-2B). Yolk sac tumors are solid, homogeneous, gray-white to tan, with a myxoid or gelatinous cut surface (Figure 24-2C). They may partially undergo cystic change. Choriocarcinomas are hemorrhagic and necrotic ill-defined masses with foci of solid gray-tan tissue, often at the periphery of the tumor. Teratomas are often nodular with heterogeneous cut surface and include solid and cystic areas (Figure 24-2D). Cysts may contain clear, flaky, gelatinous, or mucoid material. Bone, cartilage, hair, or tooth may be present. Teratomas with secondary malignant component often contain solid gray-to-white nodules with associated hemorrhage or necrosis. In regressed tumors, ill-delineated nodules with stellate or band-like scar may be present (Figure 24-2E).

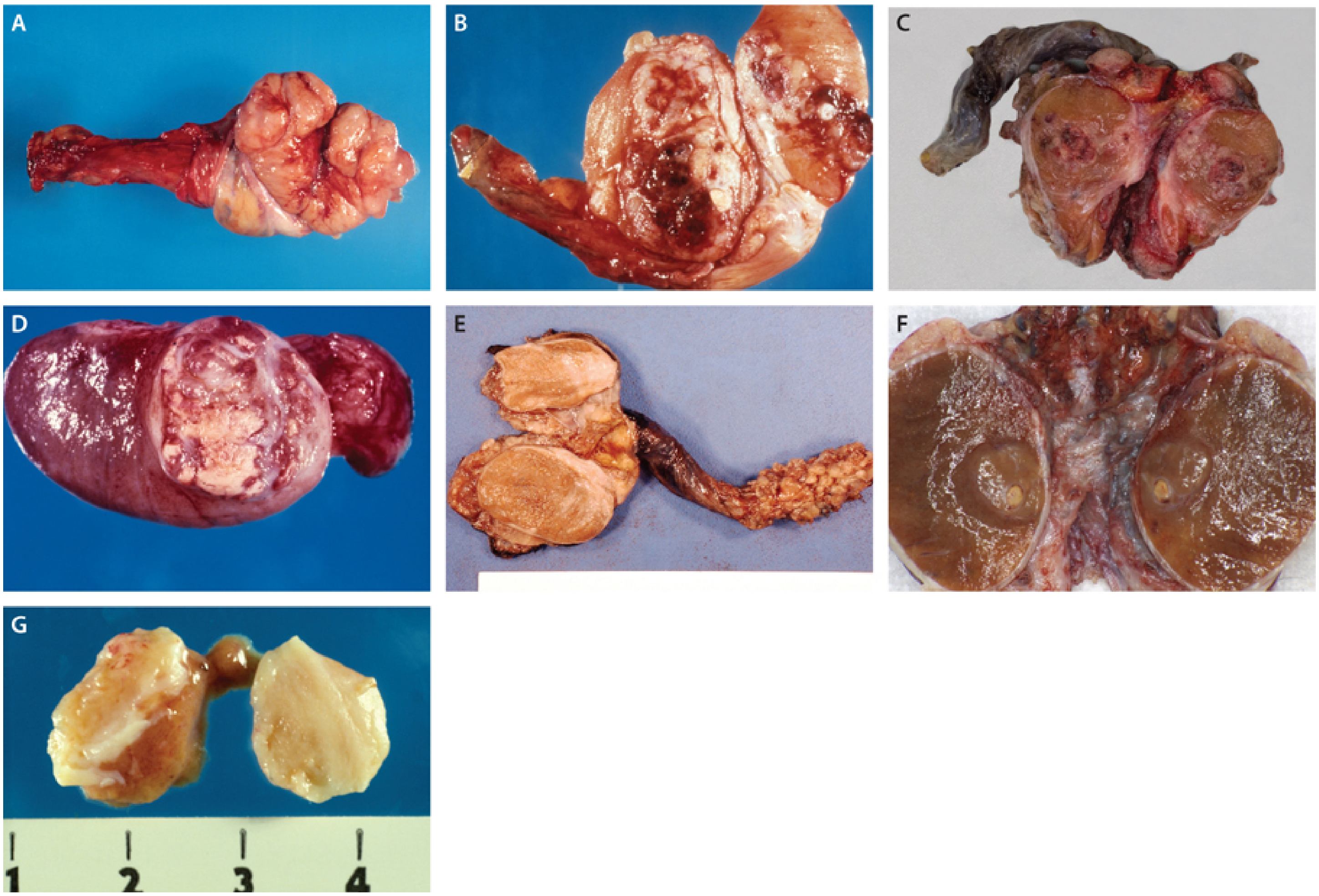


Figure 24-2. Gross morphology of germ cell tumors. A. A seminoma is shown with a lobulated homogeneous cut surface with creamy tan and white color, soft and fleshy texture, and bulging out of the surrounding parenchyma. B. An embryonal carcinoma has a variegated cut surface that is solid tan-white with hemorrhage and necrosis. C. Yolk sac tumor component in a mixed germ cell tumor appears solid, homogeneous, gray-white, and myxoid. D. Teratomas are nodular with heterogeneous cut surface and include solid and cystic areas. E. A regressed germ cell tumor is shown with ill-delineated fibrous scar. F. A Leydig cell tumor with uniform yellow-to-brown cut surface is shown. G. An adenomatoid tumor is well circumscribed with a tan homogeneous cut surface. (C: courtesy of Muhammad Idrees, MD.)

Most sex cord–stromal tumors are well circumscribed with solid cut surface and tan-to-yellow color. Leydig cell tumors have a uniform, yellow-to-brown cut surface (Figure 24-2F) and may have focal necrosis or hemorrhage. Sertoli cell tumors show a homogeneous solid, soft-to-firm, tan-to-yellow cut surface and may have focal cystic change. Adenomatoid tumors are often found in the epididymis or paratestis but are

occasionally present within the testicular parenchyma. They are well circumscribed with a tan, homogeneous cut surface (Figure 24-2G).

IV. Dissection technique of orchiectomy specimen

Thorough examination of tumor for extension beyond the testis into the hilar soft tissue (pT2), the epididymis (pT2), the tunica vaginalis (pT2), the spermatic cord (pT3), and the scrotal skin (pT4) is of critical value for the American Joint Committee on Cancer (AJCC) staging system. Blocking routine sections at the above locations will provide important staging information. Mixed GCTs contain multiple different components with grossly different appearances, and sampling of all areas is important for histologic type of the tumor.

1. Check the clinical and radiologic information, including serum tumor markers: human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH). These markers may indicate the presence of certain types of GCT in the specimen.

2. Orient the specimen. The spermatic cord emerges from the orchiectomy specimen at the superior pole of the testis and epididymis (Figures 24-1 and 24-3).

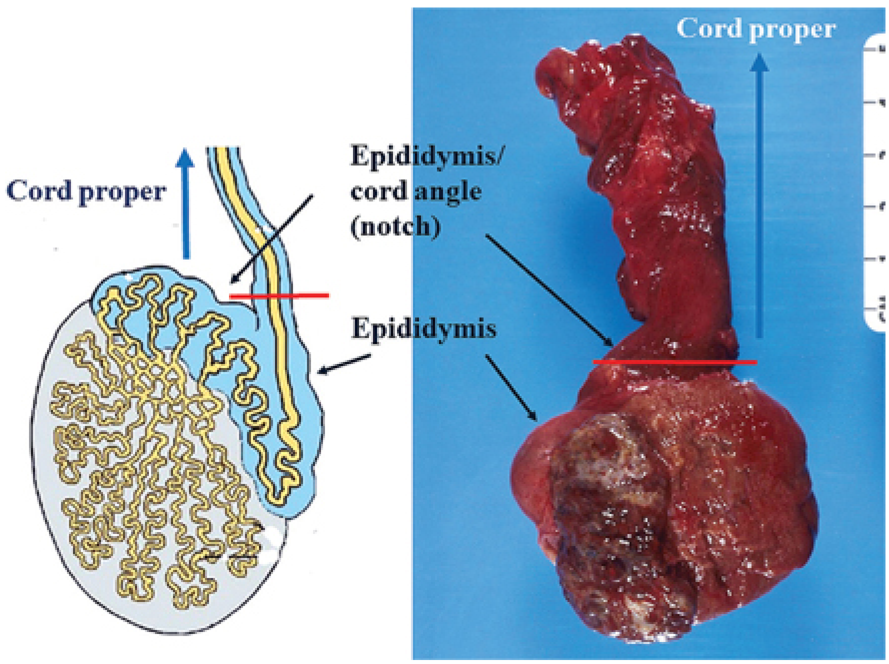


Figure 24-3. In the orchiectomy specimen (right) and diagram (left), the spermatic cord emerges at the superior pole of the testis and epididymis. The cord above the epididymis/cord angle (notch) is cord proper. When grossing a radical orchiectomy specimen, one should take first the section at the level of angle (red line). Tumor grossly extending beyond the angle (notch) is considered pT3.

3. Record the weight and size. Three dimensions of the entire specimen, the testis, the epididymis, and two dimensions of the spermatic cord should be recorded.

4. Ink the outer surface of testis and spermatic cord.

5. Take the spermatic cord margin first, followed by a section at the level of epididymis/cord angle (notch), before opening the specimen to avoid contamination by tumor cells.

6. Open and inspect the tunica vaginalis sac along the anterior border to look for any adherence to tunica albuginea indicative of tumor involvement.

7. Bivalve the testis parallel to and through the epididymis.

8. Section the testis at 5-mm intervals perpendicular to the initial section.

9. The epididymis may be sectioned from the posterior aspect and perpendicularly to its long axis, from head to tail.

10. Describe and record tumor macroscopy, including size in three dimensions, site, focality, and extent of the tumor.

- Size of the tumor in three dimensions; if multiple tumor nodules are present, size of each nodule should be recorded
- Cut surface: circumscription, encapsulation, color, consistency, necrosis, hemorrhage, calcification, cystic change
- Extent of the tumor, including extension through the tunica albuginea, invasion into the epididymis, hilar soft tissue, spermatic cord, and scrotum
- Distance of the tumor from all margins, including spermatic cord margin, tunica vaginalis, and scrotal skin

11. Obtain fresh tissue for research and/or photographs, based on institutional guidelines. Procure tissue by scraping or shaving of the cut surface, and ensure sampling methods do not compromise histopathologic examination of the tissue.

12. Fix the specimen using 10% neutral-buffered formalin.

13. Submit sections for light microscopy.

- If the tumor is small and can be submitted in 10 blocks or fewer, submit the entire tumor.
- For larger tumors, submit at least one section for every centimeter of the diameter of the tumor.
- Sections should include grossly different areas (solid, cystic, hemorrhagic, necrotic, mucoid, etc); sections to show its relation to the tunica albuginea, hilum and epididymis, and junction of the tumor and nonneoplastic testis; sections of spermatic cord at the epididymis/cord angle (notch); mid and distal cord with margin; and uninvolved testis remote from the tumor. For multiple tumor nodules, each should be sampled. If dissection reveals a scar, submit the entire lesion and sample generously the uninvolved testis.

14. Spermatic cord should be first severed at the level of epididymis/cord angle (see step 5 above and Figure 24-3), serially cross-sectioned, and representatively submitted.

- Any direct/indirect tumor nodule should be noted and sampled.
- If uninvolved, submit one section at the level of epididymis/cord angle, midsection, and distal cord margin.

15. Regional lymph nodes and fat. Record the number and size of lymph nodes, and submit all lymph nodes. Grossly positive lymph nodes may be sampled. Other lymph nodes should be entirely submitted.

Example of gross description for radical orchiectomy specimen

Specimen A: Received in formalin is the right radical orchiectomy. The specimen weighs 18 grams and measures 8.2 x 3.8 x 3.4 cm. The testis measures 5.1 (superior to inferior) x 3.3 (medial to lateral) x 3.1 (anterior to posterior) cm. The epididymis is1.2 x 1.0 x 0.7 cm. The spermatic cord is 4.5 x 1.2 x 1.1 cm.

There is a tumor in the superior half of the testis, measuring 2.2 x 2.1 x 1.4 cm. It is unifocal. The cut surface is solid, relatively homogeneous, well circumscribed, lobulated, tan, soft. Tumor necrosis is present, 10% of the tumor. Tumor extends into the hilum and the epididymis but does not extend into spermatic cord and tunica vaginalis. All surgical margins are grossly free. Tumor is 2.1 cm from spermatic cord margin, 0.6 cm from closest blue-inked tunica vaginalis margin.

The uninvolved testicular parenchyma is tan.

Ink code

The external surface of the specimen inked blue.

Section code

The tumor is entirely submitted as follows:

A1: Spermatic cord margin, en face

A2: Spermatic cord, mid section

A3: Spermatic cord, epididymis/cord angle (notch)

A4: Tumor and closest tunica vaginalis margin

A5-A6: Tumor extending into the hilum

A7-A8: Tumor extending into the epididymis

A9-A10: Tumor with tunica albuginea

A11-A12: Tumor with necrosis

A13: Tumor with hemorrhage

A14-A15: Tumor and uninvolved testis interface

A16: Uninvolved testis

A subtotal orchiectomy specimen should be handled like a radical orchiectomy specimen, with few differences. Identifying and inking the surgical resection margin with a second color is critical. Perpendicular sections of this margin should be submitted.

V. Common pathologic findings in orchiectomy specimens

GCTs are the most common tumors of the testis and are classified using the 2016 World Health Organization (WHO) system (4th ed). The most common testicular GCT is seminoma, which accounts for almost half of all GCTs. Mixed GCTs are the most common nonseminomatous tumors, with embryonal carcinoma being the most common histologic type. The majority of seminomas and almost all of the nonseminomatous tumors are associated with germ cell neoplasia in situ (GCNIS) in the adjacent parenchyma. Rarely, other testicular tumors, including sex cord–stromal tumors (Leydig cell tumor, Sertoli cell tumor, granulosa cell tumor, etc), paratesticular tumors (including adenomatoid tumors), and mesenchymal tumors may be encountered.

VI. Common potential staging pitfalls and solutions

Elevated preorchiectomy serum markers, including AFP or the beta subunit of HCG (beta-HCG), may provide clues to the histologic types of GCT components in the orchiectomy specimens. AFP is elevated in yolk sac tumor. Beta-HCG can be slightly elevated in any tumors with syncytiotrophoblast giant cells. However, significantly elevated levels of beta-HCG, often exceeding tens of thousands of milli-International Units per milliliter, indicate the presence of choriocarcinoma. Additional tissue sampling is warranted if the initial sampling fails to detect yolk sac or choriocarcinoma components when the preorchiectomy AFP or beta-HCG is significantly elevated.

Mixed GCTs contain different components that may have different gross appearances. It is important to sample all areas, including necrosis and hemorrhage, for accurate histologic classification.

GCNIS and so-called dysgenetic changes—including tubular atrophy and hyalinization, impaired spermatogenesis, immature Sertoli cells, and microlithiasis—are seen in most of and support the diagnosis of GCTs. Therefore, the testicular parenchyma adjacent to the tumor should be generously sampled.

Testicular scars may represent regressed/burnt-out testicular GCTs. It is imperative to submit the entire scarred area and amply sample the remaining parenchyma to look for features diagnostic of regressed GCT, including GCNIS, coarse intratubular calcifications within expanded tubules (dystrophic calcifications), and other findings suggestive of regressed GCTs, including lymphoplasmacytic infiltrates and prominent vascularity within the scar, and dysgenetic changes.

Tunica vaginalis invasion represents a rare route for extratesticular spread and is staged as T2. The tumor penetrates through tunica albuginea to perforate the mesothelial lining. The parietal layer of the vaginalis is often adherent to the tunica albuginea, which can be discovered by careful gross examination.

Invasion of rete testis does not assign a higher pT stage to a tumor that is otherwise limited to the testis. However, some studies suggest rete testis invasion is an adverse prognostic factor in addition to staging in pure seminomas. Therefore, a section of the rete should be submitted.

Invasion into testicular hilar soft tissue and epididymis is staged as T2. Sections should be taken to confirm the involvement of these structures.

Spermatic cord involvement contiguous with the primary testicular tumor is T3. Noncontiguous involvement of the spermatic cord results from vascular invasion and is staged as pM1 if the tumor thrombus invades into the perivascular soft tissue. It is therefore critical to distinguish contiguous and discontiguous cord involvement by taking a section at the epididymis/cord angle (notch).

An accurate size measurement is important for pure seminomas because T1 seminoma is substaged into pT1a and pT1b with the cutoff of 3 cm.

Size and number of the involved lymph nodes and extranodal extension are factored in the N stage of lymphadenectomy specimens.

VII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, tumor site and size, histologic type, tumor extension, margins status, lymphovascular invasion, nodal involvement, and pathologic staging. The serum markers status and any additional pathologic findings may also be incorporated into the report.

Standard pathology report

Final diagnosis

Left testis and spermatic cord, radical orchiectomy

- Classical seminoma, 4.3 cm in greatest dimension
- Tumor invades the epididymis
- No lymphovascular invasion identified
- Spermatic cord and tunica vaginalis surgical resection margins negative for the tumor
- GCNIS is present
- AJCC TNM stage: pT2 NX S0

Synoptic report

Specimen laterality: Left
Tumor focality: Unifocal
Tumor size
  Greatest dimension of main tumor mass: 4.3 cm
  Additional dimensions: 3.5 x 2.9 cm
Histologic type
  GCNIS
  Seminoma
Tumor extension: Tumor invades epididymis
Margins
  Spermatic cord margins: Uninvolved by tumor
  Tunica vaginalis: Uninvolved by tumor
Lymphovascular invasion: Not identified
Pathologic stage classification (pTNM, AJCC 8th ed)
  Primary tumor (pT): pT2
  Regional lymph nodes (pN): pNX: Cannot be assessed
  Distant metastasis (pM): Not applicable
Preorchiectomy serum tumor markers: Within normal limits
Postorchiectomy serum tumor markers: Within normal limits
Serum tumor markers
    S0: Serum marker study levels within normal limits Additional pathologic findings
    GCNIS
    Seminiferous tubule atrophy and fibrosis
Comment: Blocks A4 and A5 may be used for future ancillary studies, if needed.

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25. Ureter and Renal Pelvis

Sasan Setoodeh, MD; Ming Zhou, MD, PhD

This chapter discusses the grossing and handling of nephroureterectomy and segmental ureterectomy that are performed for urothelial carcinoma of the upper urinary tract, including renal pelvis and ureter. Readers are referred to the American Joint Commission on Cancer (AJCC) staging manual,[1] the World Health Organization (WHO) classification of upper tract tumors,[2] and the College of American Pathologists (CAP) cancer protocols[3] for detailed discussion of diagnosis, classification, specimen handling, staging, and reporting.

I. Indication for ureterectomy/nephroureterectomy

- Radical nephroureterectomy with complete resection of bladder cuff: high risk upper tract urothelial carcinomas
- Segmental ureterectomy: noninvasive low-grade urothelial carcinomas that cannot be managed with endoscopic resection because of multifocality or large tumor size; and high-grade or invasive tumors when preservation of renal function is a goal

II. What do we expect to see in the ureterectomy/nephroureterectomy specimens?

A segmental ureterectomy specimen consists of a portion of the ureter. A bladder cuff may be included in the distal segmental ureterectomy. A radical nephroureterectomy specimen usually consists of the kidney, the ureter, and the bladder cuff. Regional lymph nodes may be submitted for pathologic examination.

III. Typical macroscopic appearance of upper urinary tract tumors

Urothelial carcinomas can be unifocal or multifocal with skip areas. Most are friable polypoid or papillary tumors but sometimes may be sessile (Figures 25-1 and 25-2), nodular, ulcerated, or infiltrative. They may completely fill the lumen of the ureter and expand the structure and may even become a scirrhous mass. Invasion into the surrounding soft tissue or kidney parenchyma may be present. Urothelial carcinoma in situ may be noted as erythematous patches on the mucosa. Squamous cell carcinomas of the urinary tract often fill the ureteral lumen with a bulky polypoid or solid necrotic mass.

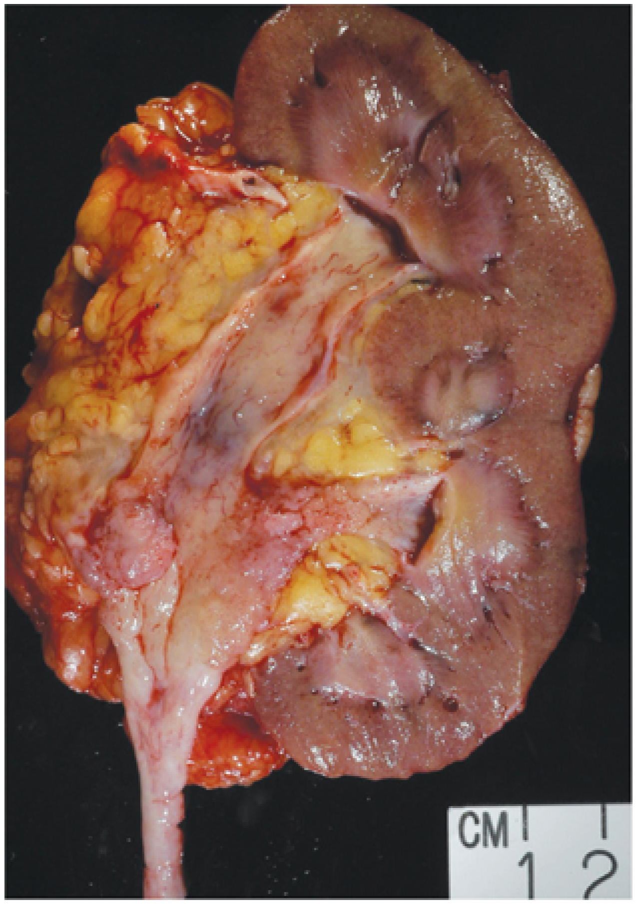

Figure 25-1. A bivalved radical nephrectomy specimen showing several sessile polypoid tumors in the renal collecting system.

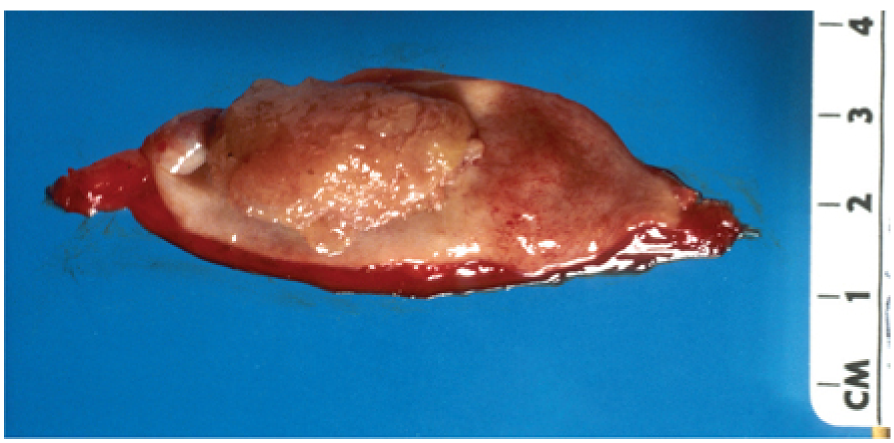

Figure 25-2. A segmental ureterectomy specimen showing a polypoid tumor expanding the ureteral lumen.

IV. Dissection technique of ureterectomy/nephroureterectomy specimen

1. Check the clinical and radiologic information.
- History of prior diagnosis pertaining to the location of the tumor and treatment.
- Hereditary nonpolyposis colon cancer (HNPCC) syndrome (Lynch syndrome II) is associated with upper tract urothelial carcinomas.

2. Review the AJCC TNM staging criteria for upper tract tumors.
3. Orient the specimen.
- Nephroureterectomy: the ureter courses downward from the renal hilum; identify the bladder cuff at the end of the ureter.
- Ureterectomy: orientation is often marked by surgeons with sutures.

4. Record the weight and size.
- Three dimensions of the entire specimen and the kidney, and two dimensions of the ureter, renal vein, and renal artery should be recorded.

5. Ink the specimen.

a) Ink the margins of the ureter or the urinary bladder cuff.
- For ureterectomy, ink in different colors the proximal and distal ureteral margins. Ink the outer surface of the ureter in a different color.

b) For nephroureterectomy, ink in different colors the entire outer surface of the Gerota fascia and renal sinus fat margin.

6. Sample margins.

a) Ureterectomy: Shave both proximal and distal ureteral margins.

b) Nephroureterectomy: Bladder cuff margin should be sampled en face; also shave the renal artery and renal vein margins.

7. Opening and fixing specimens.

a) Ureterectomy
- Palpate the ureter to try to locate the tumor.
- Open the ureter longitudinally. If the tumor is palpable or visible, avoid cutting through the tumor.
- Pin the specimen on a foam board and fix for a few hours.

b) Nephroureterectomy
- Insert a probe into the ureter or the renal vein as the guiding plane to bivalve the kidney. Bivalving from the lateral aspect is not preferred. Alternatively, cut open the ureter longitudinally from the distal tip to the ureteropelvic junction and the renal calyces, and then bivalve the kidney
- Fix overnight.

8. Describe and record tumor macroscopy, including site, size, focality, appearance, ulceration, and necrosis.
- Size of the tumor in three dimensions
  - If the tumor is multifocal, the largest size and the range should be recorded.
- Tumor may vary from papillary to polypoid or flat and ulcerated
- Gross extent of the tumor: sectioning through the tumor after fixation to determine the deepest extent of invasion, involvement of the kidney, or the perirenal soft tissue
- Distance of the tumor from margins
  - Distal ureter (and proximal ureter in ureterectomy) margin
  - Closest Gerota fascia margin
  - Closest hilar soft tissue margin

9. Describe the uninvolved kidney (nephroureterectomy).
- Presence of other findings: cysts, calculi
- Color, thickness of cortex, distinction of corticomedullary junction, shape of renal papillae

10. Obtain fresh tissue for research, based on institutional guidelines.
- Ensure sampling methods do not compromise histopathologic examination of the tissue

11. Submit sections for light microscopy.
- At least one section per centimeter of tumor, to include:
  - Deepest invasion
  - Tumor and the adjacent renal parenchyma
  - Tumor and the perirenal adipose tissue (nephroureterectomy)
  - Tumor and the renal sinus interface (nephroureterectomy)
  - Tumor and the periureteral soft tissue (ureterectomy)
- Any different-appearing mucosa should be submitted
  - Erythematous areas may indicate carcinoma in situ (CIS)
- Margins
  - Bladder cuff, ureter(s), renal vein, renal artery, perirenal/periureteral soft tissue

- Uninvolved renal pelvis or ureter
- Uninvolved kidney (nephroureterectomy)

12. Palpate and submit all hilar and perirenal lymph nodes.

- Submit one section from each grossly positive lymph node
- All other lymph nodes should be entirely submitted

13. Describe the adrenal gland, if present (nephroureterectomy).

- Size, color, nodularity
- Submit sections from the grossly involved and the uninvolved adrenal gland

Example of gross description for ureterectomy/nephroureterectomy specimen

Received in formalin is a radical nephroureterectomy specimen consisting of right kidney with attached ureter and the bladder cuff. The specimen weighs 215 grams and measures 18 x 13 x 12 cm. The kidney is 11 x 9 x 7 cm. The ureter is 20 cm in length and 1.1 cm in diameter. The bladder cuff is 1.9 x 1.0 x 0.8 cm. Renal vein is 2.0 cm in length and 1.2 cm in diameter. Renal artery is 1.0 cm in length and 0.7 cm in diameter.

There is a pink-grey papillary mass in the renal pelvis and upper major calyx. It measures 2.9 x 2.5 x 1.1 cm. It is unifocal. Grossly the tumor invades the renal pelvic wall with maximal depth of invasion of 0.5 cm. Tumor also invades into renal parenchyma. All surgical margins, including ureteral, renal vein, renal artery, and perirenal soft tissue, appear negative. The tumor is 20 cm from the distal ureteral margin.

Other ureteral or pelvicalyceal lesions include a 0.8 x 0.7 cm, flat, granular, erythematous, mucosal lesion in the ureter at the ureteropelvic junction.

Uninvolved kidney has a cortical thickness of 0.9 cm. Corticomedullary junction is well defined. Adrenal gland is not present. Lymph nodes are not identified.

Ink code

Bladder cuff margin: red

Ureter: blue

Perirenal soft tissue: black

Section code

A1: Bladder cuff margin, en face

A2: Renal vein and artery margins

A3-A5: Tumor, representative sections, including maximal depth of invasion

A6: Tumor and renal sinus interface

A7: Tumor and uninvolved kidney interface

A8: Tumor and adjacent soft tissue margin

A9 -A10: Erythematous mucosa, ureteropelvic junction

A11: Uninvolved renal pelvic, inferior major calyx

A12: Uninvolved ureter, upper third, representative sections

A13: Uninvolved ureter, middle third, representative sections

A14: Uninvolved ureter, lower third, representative sections

A15: Normal kidney, representative section

V. Common pathologic findings in ureterectomy/nephroureterectomy specimens

The majority of the tumors of the upper urinary tract are urothelial carcinomas, classified using the same histopathologic subtypes as in the urinary bladder, according to the 2016 WHO classification system (4th ed). Other subtypes are less frequent, including squamous cell neoplasms, adenocarcinomas, neuroendocrine tumors, and metastatic tumors. The specimens with the urothelial carcinomas may contain associated epithelial lesions, including carcinoma in situ (CIS), papillary urothelial neoplasm of low malignant potential (PUNLMP), or urothelial papilloma. Additional nonneoplastic pathologic findings in the ureter may include cystitis cystica et glandularis, squamous metaplasia, or inflammation.

VI. Common potential staging pitfalls and solutions

The depth and extent of invasion into the subepithelial connective tissue/lamina propria (pT1), muscularis propria (pT2), or beyond (pT3 or pT4) is the most important prognostic factor for patients with upper urinary tract tumors. Identifying and submitting the site of the deepest tumor extension within the wall of the ureter and renal pelvis and the involvement of renal parenchyma are of paramount importance.

The regional lymph nodes for the renal pelvis are renal hilar, paracaval, aortic, and retroperitoneal. The regional lymph nodes for the ureter are renal hilar, iliac, paracaval, periureteral, and pelvic. Involvement of lymph nodes beyond the regional lymph nodes is considered distant metastasis (M1).

VII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, tumor site and size, histologic type, histologic grade, tumor configuration, tumor extension, margins status, nodal involvement, pathologic staging, and pathologic findings in the nonneoplastic renal tissue. The presence of associated epithelial lesions, lymphovascular invasion, extranodal extension, and additional pathologic findings may also be incorporated into the report.

Standard pathology report

A. Left distal ureter, ureterectomy
- Invasive high-grade papillary urothelial carcinoma
- Tumor invades into muscularis propria
- Both proximal and distal margins are negative for tumor
- AJCC stage: pT2 N0

B. Left pelvic lymph nodes, excision
- Three lymph nodes negative for metastatic carcinoma (0/3)

Synoptic report

Procedure: Ureterectomy
Specimen laterality: Left
Tumor site: Ureter
Tumor size: 7 cm
Histologic type: Urothelial carcinoma
Histologic grade: High grade
Tumor extension: Tumor invades the muscularis
Tumor configuration: Papillary
Margins: Uninvolved by invasive carcinoma and carcinoma in situ/noninvasive urothelial carcinoma
Lymphovascular invasion: Not identified
Regional lymph nodes
  Number of lymph nodes involved: 0
  Number of lymph nodes examined: 3
Pathologic stage classification (pTNM, AJCC 8th ed)
  Primary tumor (pT): pT2
  Regional lymph nodes (pN): pN0
Additional findings
  Associated epithelial lesions: None identified
Additional pathologic findings: Inflammation/regenerative changes
Comments: Blocks A2 and A3 may be used for future ancillary studies or research.

References

1. McKiernan JM, Hansel DE et al. Renal pelvis and ureter. In: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017:757-764.
2. Humphrey PA, Moch H, Reuter VE, Ulbright TM, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs.* 4th ed. Geneva, Switzerland: WHO Press; 2016:77-134.
3. Paner GP, Humphrey PA, Zhou M, et al. Protocol for the Examination of Specimens From Patients With Carcinoma of the Ureter and Renal Pelvis. College of American Pathologists. 2019. Available at www.cap.org/cancerprotocols. Accessed May 27, 2020.

26. Urethra

Sasan Setoodeh, MD; Ming Zhou, MD, PhD

The urethral involvement by bladder urothelial carcinomas occurs in approximately 8.1% of male patients and is rare in female patients. Urethrectomy is the choice of treatment in those who develop invasive urethral recurrences and offers long-term survival benefits.[1] Localized noninvasive tumors of the distal urethra may be resected transurethrally. Invasive tumors are treated with total urethrectomy, concurrently with penectomy, cystectomy, cystoprostatectomy, anterior exenteration, or as salvage surgery.

I. Indication for urethrectomy

- Urethral tumors, primary or recurrence from the bladder primary
- Partial urethrectomy for urethral stricture

II. What do we expect to see in the urethrectomy specimens?

A total urethrectomy specimen includes the entire length of the urethra and surrounding soft tissue. In men, it consists of the penile, bulbomembranous, and prostatic urethra and may have attached cystectomy, cystoprostatectomy, and penectomy specimens. Partial urethrectomy contains a segment of the urethra, usually the distal urethra with the surrounding tissue.

III. Typical macroscopic appearance of urethral tumors

Urethral carcinomas are typically exophytic, papillary, and whitish with erythematous areas, but they may also show a nodular infiltrative appearance with ulceration (Figure 26-1). Squamous cell carcinomas may have a bulky, polypoid, solid, and necrotic appearance. Adenocarcinoma of the urethra commonly shows large exophytic or nodular tumors with cystic or gelatinous appearance.

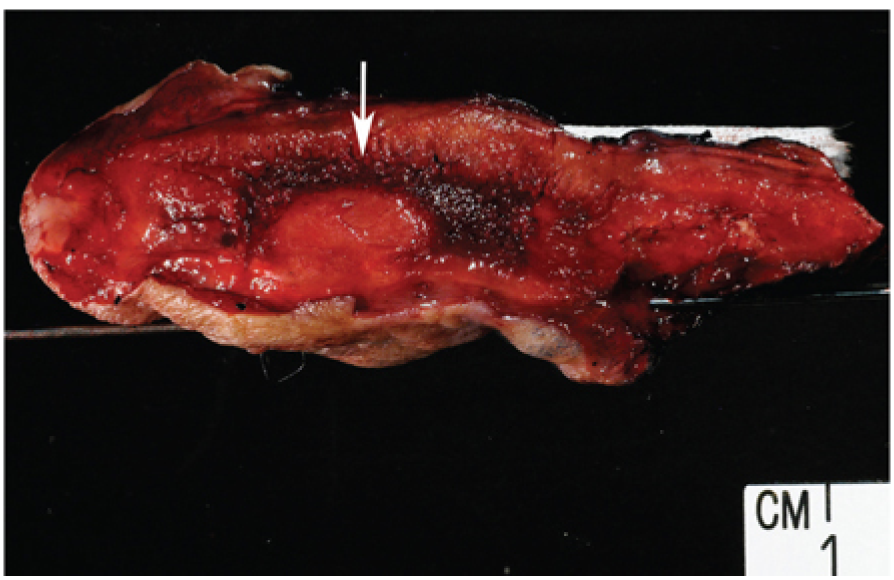

Figure 26-1. A partial penectomy specimen showing a urethral cancer infiltrating into the corpus cavernosum (arrow).

IV. Dissection technique of urethrectomy specimen

1. Check the clinical and radiologic information for:

a) History of prior diagnosis pertaining to the location of the tumor, and treatment

2. Review the American Joint Committee on Cancer (AJCC) TNM staging system for urethral tumors.

3. Orient the specimen.

a) For urethrectomy attached with other resected organs, orientation is straightforward by using other organs as reference.

b) Orientations of the urethrectomy specimen should be marked by surgeon.
4. Record the weight and size.
a) Record three dimensions of the entire specimen and each organ.
b) Weight is required if other organs (eg, prostate) are present.
5. Ink the specimen.
a) Ink the proximal and the distal urethral margins in different colors.
- Urethral mucosal margins may retract and should be identified.
- Ink the margins of other organs (prostate, bladder, vagina, etc) accordingly.

b) Ink the circumferential soft tissue margin.
6. Dissection
a) Open the specimen longitudinally and inspect for lesions.
b)Describe and record tumor macroscopic features, including size, site, focality, texture, consistency, color, necrosis, and ulceration.
- Gross extent of the tumor
  - Invasion into the urethral wall and periurethral tissue, and depth of invasion
  - If other organs and structures are present, record the extent of tumor into those organs and structures (corpus spongiosum, corpus cavernosum, prostate, vagina, bladder, etc)
- Distance of the tumor from margins
  - Distal and proximal margins
  - Circumferential soft tissue margins

c) Describe the other findings.
- Cysts, calculi

7. Photograph the specimen and the tumor.
8. Obtain fresh tissue for research, based on institutional guidelines.
- Ensure sampling methods do not compromise histopathologic examination of the tissue

9. Submit sections for histologic examination.
a) Margins
- Proximal margin, distal margin, and circumferential soft tissue margins
- En face, perpendicular if tumor is close to the inked margin

b) At least one section per centimeter of tumor to include:
- Deepest invasion
- Tumor and the adjacent anatomic landmarks (corpus spongiosum, corpus cavernosum, prostate, periurethral muscle, vagina, and bladder)

c) Any different-appearing mucosa
d) Uninvolved urethra
- Submit proximal and distal sections, if possible.

10. Submit regional lymph nodes.
a) Submit one section from each grossly positive lymph node.
- Record the size of grossly positive lymph nodes.

b) All other lymph nodes should be entirely submitted.
- The presence of nodal disease may be used as an indication for adjuvant therapy.

Gross description for urethrectomy specimen

The following example describes a radical cystectomy with urethrectomy. Readers are referred to the chapters on cystectomy (chapter 27) and penectomy (chapter 22) for detailed description of handling and grossing of cystectomy and penectomy specimens. This example focuses on the urethrectomy specimen.

Specimen A: Received in formalin is a cystectomy specimen with urethrectomy which consists of urinary bladder, bilateral ureter stumps, and urethra. Overall the specimen measures 16 cm (superior-inferior) x 10 cm (right-left) x 3.5 cm (anterior-posterior). Bladder measures 11 cm superior to inferior), 10 cm (right to left), and

3.5 cm (anterior to posterior). Right ureter is 2.5 cm in length and 0.3 cm in diameter, and left ureter is 2.4 cm in length and 0.3 cm in diameter. Urethra is 5 cm in length and 1.2 cm in diameter.

There is a tumor in the right lateral wall of the bladder that measures 2.1 x 1.5 x 1.2 cm. It is sessile with surface ulceration and is tan and solid. The tumor invades the inner half of the muscularis propria and invades 0.7 cm into the muscularis propria. It is otherwise confined to the bladder. It is 0.5 cm from the right ureteral orifice. It does not involve ureters or other organs.

In the uninvolved bladder mucosa there is an area of erythematous granular mucosa at the dome, 0.5 x 0.5 cm. Diffuse erythematous granular mucosa involves the trigone and extends into the urethra.

Both ureteral orifices and ureters are probe patent. There is no tumor nor stricture.

In the urethra, the mucosa is patchy granular and erythematous mucosa. There are two small papillary lesions, 0.8 and 0.7 cm, respectively, in anterior wall, 1.0 and 1.8 cm from the urethrovesical junction and 3.2 cm and 2.5 cm from the distal urethral margin. Both lesions are confined to the mucosa

Ink code

Anterior bladder and urethra: green
Posterior bladder and urethra: black
Distal urethra: yellow

Section code

Partially submitted as follows:
A1: Distal urethral resection margin, en face
A2: Right ureteral edge, en face
A3: Left ureteral edge, en face
A4: Bladder tumor showing deepest muscularis propria invasion
A5-A8: Representative tumor sections
A9: Right ureteral orifice
A10: Left ureteral orifice
A11: Erythematous mucosa at the dome
A12: Uninvolved mucosa left lateral wall
A13: Uninvolved mucosa right lateral wall
A14: Uninvolved mucosa posterior wall
A15: Uninvolved mucosa anterior wall
A16: Uninvolved mucosa at the dome
A17: Urethra, first papillary lesion
A18: Urethra, second papillary lesion
A19: Urethra, erythematous flat area
A20: Urethra, uninvolved mucosa

V. Common pathologic findings in urethrectomy specimens

Most urethral tumors represent extension of bladder urothelial carcinomas. Primary tumors without a bladder primary or those arising in the periurethral glands are exceedingly rare. In women, squamous cell carcinoma is the most common histologic subtype and is most common in the anterior urethra (distal third). Urothelial carcinoma is next in frequency, followed by adenocarcinoma. A significant proportion of adenocarcinomas in women are clear cell adenocarcinomas, but these are quite rare in men. In men, most tumors involve the bulbomembranous urethra, followed by penile urethra and prostatic urethra. Most carcinomas of the male urethra are squamous cell carcinoma, followed by urothelial carcinoma. As in women, urothelial carcinomas are typically more proximal. Primary urethral adenocarcinomas are rare in men. Periurethral glands of Skene in females and Cowper and Littre in males give rise to the rare adenocarcinoma of the urethra.

Squamous or glandular differentiation in urothelial carcinoma is not uncommon. Per the 2016 World Health Organization (WHO) classification, a pure histology of squamous cell carcinoma, adenocarcinoma, or Müllerian type is required to designate a tumor as such, and all others with recognizable papillary, invasive, or flat

carcinoma in situ (CIS) urothelial component may be considered as urothelial carcinoma with divergent differentiation.

VI. Common potential staging pitfalls and solutions

The involvement of the surrounding structures (corpus spongiosum, corpus cavernosum, prostate, periurethral muscle, vagina, and bladder) and the depth of invasion are critical for proper pathologic staging for tumors of the urethra. Careful examination of tumor and the adjacent tissues, proper fixation, and appropriate sectioning of the tumor are needed for the accurate staging of the tumor. The prostatic urethra has different AJCC staging criteria from that of the penile urethra and female urethra. In the prostatic urethra, invasion into the prostate stroma may arise from the direct extension from the urethral mucosal surface or by invasion from prostatic ducts that are colonized by urothelial carcinoma. The pT1 designation should only be applied to tumors that invade urethral subepithelial tissue immediately underlying the urothelium; invasion arising from the prostatic ducts is designated as at least pT2.

Involvement of the distal urethra by a large tumor, particularly squamous cell carcinoma, poses a particular challenge to identifying its primary location in men because the tumor may arise in the glans penis or in the distal urethra. History of bladder involvement and careful gross evaluation and sampling of the adjacent urethral mucosa and glans penis mucosa to identify in situ lesions may provide clues to its anatomic origin.

VII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, tumor site and size, histologic type and grade, tumor configuration and extension, margins status, nodal involvement, and pathologic staging. The presence of associated epithelial lesions, lymphovascular invasion, extranodal extension, and any additional pathologic findings may also be incorporated in the report.

Standard pathology report

Final pathologic diagnosis:

Bladder and urethra, radical cystectomy and urethrectomy

- Invasive high-grade urothelial carcinoma, with focal micropapillary component, forming a 2.1-cm tumor mass in the right lateral wall of the bladder
- Tumor invades the inner half of the muscularis propria
- Urothelial CIS involving the right lateral wall
- Lymphovascular invasion is present
- All ureteral, urethral, and soft tissue resection margins negative for the tumor
- Two noninvasive high-grade papillary urothelial carcinomas (0.8 and 0.7 cm, respectively) in the urethra
- Urothelial CIS in the urethra
- Pathologic stage for bladder tumor: pT2a N0
- Pathologic stage for urethral tumor: pTa N0

Synoptic report for urethral tumor

Procedure: Urethrectomy with cystectomy Tumor site:

Anterior urethra

Tumor size:

Greatest dimension (centimeters): 0.8 and 0.7 cm

Histologic type: Papillary urothelial carcinoma, noninvasive

Associated epithelial lesions: None identified

Histologic grade: High grade

Tumor configuration: Papillary, flat

Tumor extension: Noninvasive papillary carcinoma

Margins: Uninvolved by invasive carcinoma and CIS/noninvasive urothelial carcinoma

Lymphovascular invasion: Not identified
Regional lymph nodes:
  Number of lymph nodes involved: 0
  Number of lymph nodes examined: 9
TNM descriptors: m (multiple primary tumors)
Primary tumor (pT): pTa
Regional lymph nodes (pN) pN0
Additional pathologic findings: None

References

1. Nieder AM, Sved PD, Gomez P, Kim SS, Manoharan M, Soloway MS. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology*. 2004;64:950-954.
2. Humphrey PA, Moch H, Reuter VE, Ulbright TM, eds. *World Health Organization (WHO) Classification of Tumours. Pathology and Genetics of the Urinary System and Male Genital Organs.* 5th ed. Geneva, Switzerland: WHO Press; 2016:77-133.
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4. Paner GP, McKenney JK, Zhou M, et al. Protocol for the Examination of Specimens From Patients With Carcinoma of the Urethra and Periurethral Glands. College of American Pathologists. 2020. Available at www.cap.org/cancerprotocols. Accessed July 27, 2020.

27. Urinary Bladder

Sasan Setoodeh, MD; Qihui (Jim) Zhai, MD; Ming Zhou, MD, PhD

Urinary bladder resection specimens include partial, total, and radical cystectomy; radical cystoprostatectomy; and anterior exenteration. Implying partial or complete removal of the urinary bladder and/or adjacent organs such as the prostate in men, cystectomy is still one of the most effective modalities to manage a subset of patients with urothelial bladder cancer. Yet it is a dramatic procedure that has a significant impact on the patient's quality of life. Pathologic examination is the gold standard for carcinoma staging, which offers critical information for the prognosis, therapeutic choices, and future care of the patient. Appropriate handling of the specimen is the first step and serves as the foundation for the staging process. The pathology report is not only a medical but also a legal document for future therapeutic protocols. Pitfalls exist when difficult settings are encountered. We will discuss in detail appropriate specimen handling and the pertinent information to include in the pathology report.

I. Indications for cystectomy/cystoprostatectomy/anterior exenteration

Radical cystectomy is recommended for the majority of patients with muscle-invasive bladder cancer with a curative intent. Other indications include high-risk and recurrent noninvasive bladder cancers, bacillus Calmette-Guérin (BCG)–resistant carcinoma in situ (CIS), high-risk superficially invasive high-grade bladder cancer, and extensive papillary disease that cannot be managed with transurethral resection and intravesical therapy alone. Partial cystectomy is often performed for urachal tumors.

II. What do we expect to see in the cystectomy specimens?

Cystectomy specimens contain the bladder with segments of bilateral ureters and perivesical adipose tissue. Depending on the type of procedure, they may also contain prostate and seminal vesicles and vasa deferentia (in males) or anterior vaginal wall with/without uterus (in females), and part or entire urethra. Partial cystectomy is usually performed for urachal tumors and often contains a portion of the bladder dome and attached urachal remnant tissue. Umbilicus may be included in the specimen. Surgical clips or sutures may be present to mark the end of the ureters and other surgical margins.

III. Typical macroscopic findings of cystectomy specimens

Gross examination is critical, particularly in noting tumor areas with different appearances, depth of invasion within the bladder wall, and extension into adjacent structures. Invasive urothelial carcinomas may be papillary, polypoid, sessile, and ulcerated; and multifocality is not uncommon (Figure 27-1). In situ component may appear as erythematous, raised, velvety, or granular areas grossly. Squamous cell carcinoma (SCC) of the bladder is typically a bulky, polypoid, solid, tan-white mass with ulceration and necrosis. The presence of keratin debris and necrotic material are indicators of SCC. A mucoid appearance on the cut surface of bladder tumors may be observed in adenocarcinomas of the bladder. The tumor may invade the bladder muscular wall and perivesical adipose tissue. It is not uncommon that a cystectomy specimen does not have grossly visible residual tumor with only superficial and sometimes deep ulcer after preoperative therapy.

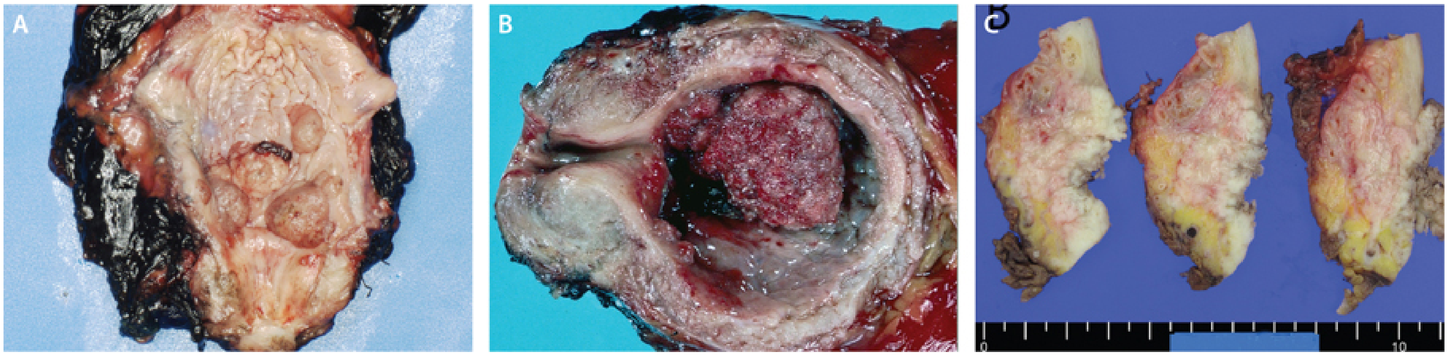

Figure 27-1. A. This radical cystoprostatectomy specimen shows multifocal, high-grade, invasive, papillary, urothelial carcinoma on the posterior and lateral wall. B. A large tumor arising in the posterior and right lateral wall is shown. Also note the erythematous and granular mucosa involved by carcinoma in situ in the lateral walls. C. Sections through a tumor show invasion into the perivesical fat.

IV. Dissection techniques: step-by-step description Transurethral resection of bladder tumor (TURBT)

The number, size, color, and consistency of tissue fragments should be recorded, and the specimen may be submitted entirely in up to 10 cassettes. If, by the initial sampling, the tumor is noninvasive or superficially invasive or contains variant histology such as adenocarcinoma, additional sampling may be needed.

Cystoprostatectomy

1. Check the clinical and radiologic information.

- Look up the prior biopsy/TURBT report or imaging for the location(s) of the tumor.
- History of precystectomy treatment.

2. Review the American Joint Committee on Cancer (AJCC) TNM staging system for bladder tumors to familiarize with the pathologic staging parameters.

3. Orient the specimen (Figure 27-2).

- The peritoneum extends further down posteriorly than anteriorly.
- The seminal vesicles are located at the posterior aspect.
- The ureters are located within the lateral perivesical fatty tissue.

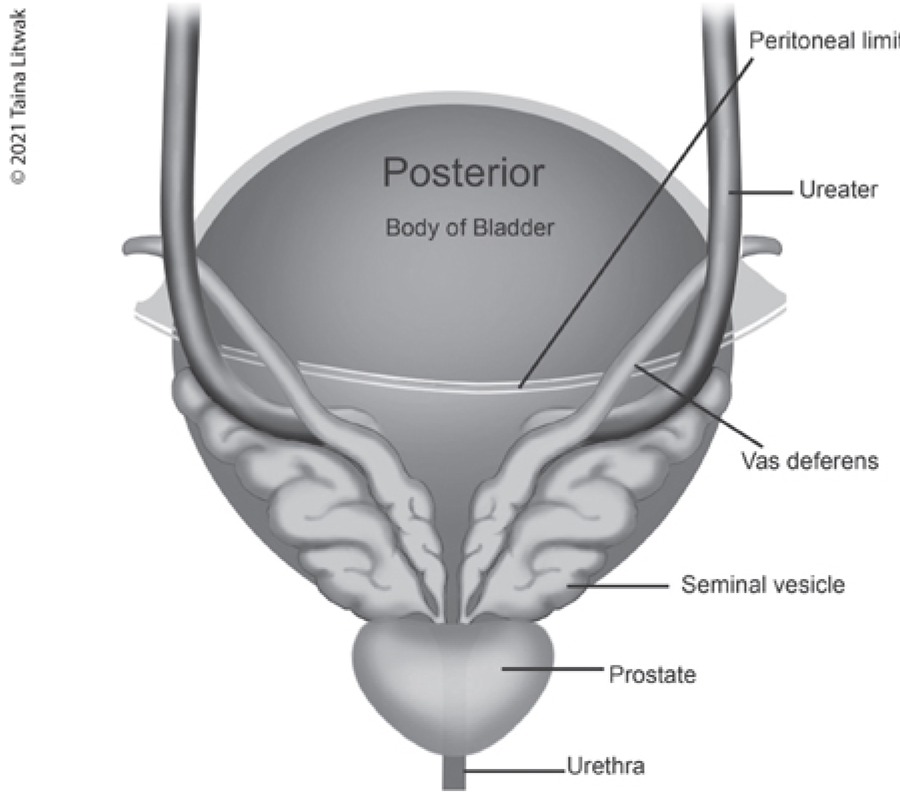

Figure 27-2. Seminal vesicles, ureters, and peritoneal reflection can be used as reliable anatomic landmarks to recognize the posterior aspect of bladder.

4. Record the weight and size
- Three dimensions of the entire specimen, bladder, ureteral stamps, and other organs if present (prostate, uterus, fallopian tubes, ovaries, etc), separately.

5. Ink the specimen.
- Ink the anterior and posterior surfaces of the bladder in different colors.
- Ink the right and left sides of the prostate gland in different colors.
- Ink other structures appropriately.

6. Shave the bilateral ureteral and distal urethral margins (if not separately submitted or evaluated intraoperatively).
- Submit the margins in their entirety.
- If there is obvious tumor involving the ureters close to the margin, perpendicular sections of the bilateral ureteral margins should be submitted.
- For distal urethral margin, amputate the distal apex of the prostate; then section this apical cone at right angles to the cut edge in thin, parallel sections. These sections will include the distal portion of the prostatic urethra and will permit precise determination of the status of the distal margin at the prostatic apex.

7. Open the bladder from the urethral end on the anterior surface (Figure 27-3A).

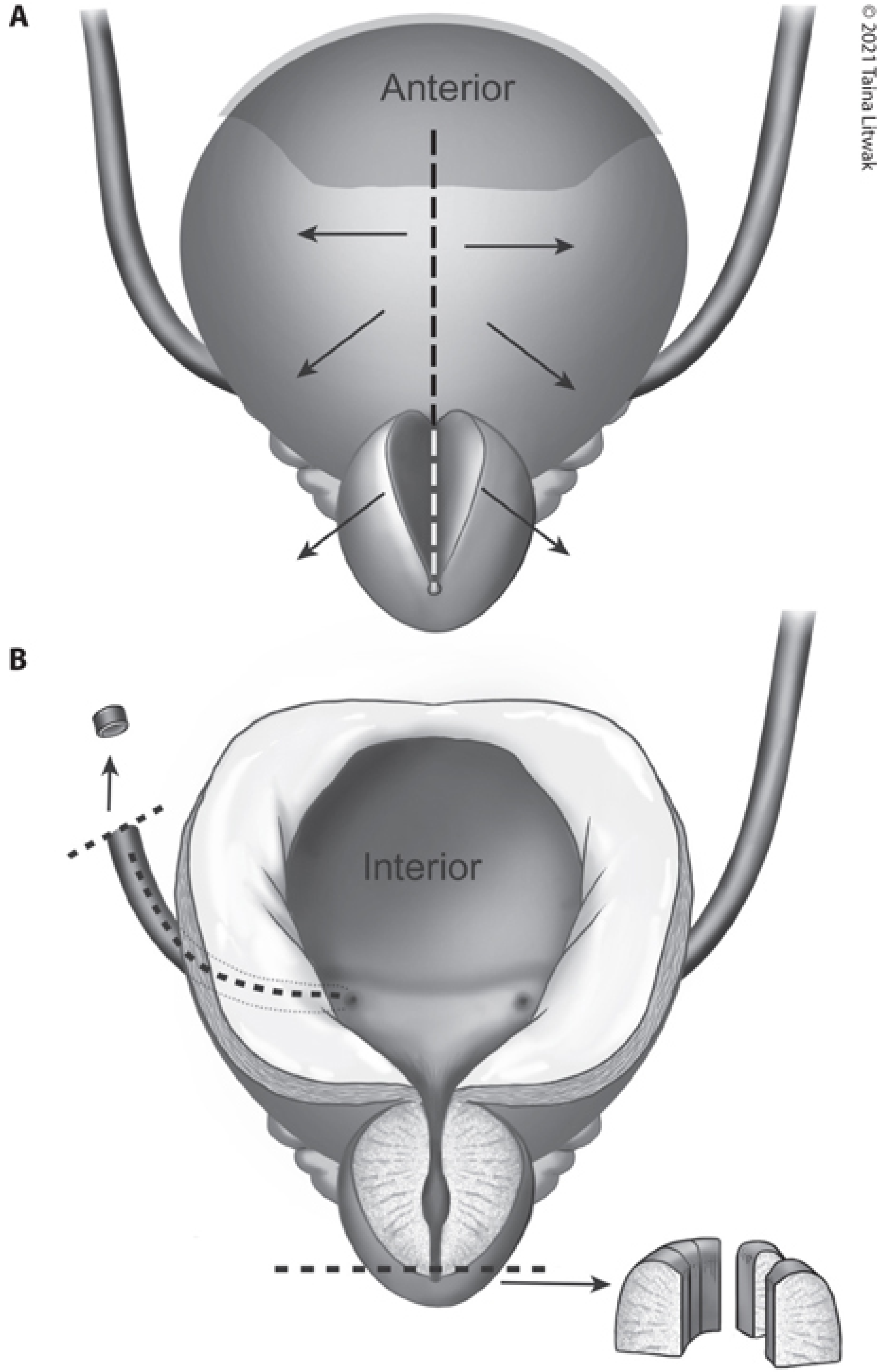

Figure 27-3. Gross dissection of a cystoprostatectomy specimen. A. The specimen is opened along the anterior surface. B. Ureters are opened along their length from the trigonal orifices. The distal urethra and prostate apex are amputated and sectioned for examination of distal urethral mucosal and prostate apical margins.

- Create a T or Y shape on the anterior surface of the bladder.
- Avoid disrupting the ureteral orifices in the posterior wall.
- Avoid cutting through the tumor (location may be known on the basis of the previous biopsy or imaging report).

8. Identify the tumor. Urothelial carcinoma can be papillary, ulcerative, exophytic, or within the wall of the bladder.

- If no obvious tumor is present, effort should be made to identify any abnormal mucosal appearance at the site of previous biopsy/resection.

9. Evaluate the rest of the bladder mucosa for subtle, flat, mucosal alterations.

10. Photograph the lesion(s).

11. Procure fresh tissue for research/tissue banking on the basis of institutional guidelines if the tumor is grossly present. Document the "cold ischemia time."

- Sample by scraping or shaving.
- Ensure sampling methods do not compromise histopathologic examination.

12. Fix the specimen for several hours to overnight using 10% neutral-buffered formalin. Even after fixation for a few hours, it is much easier to sample the urothelial mucosa and tumor, and the subsequent microscopic staging probably will be much more accurate.

13. Perform macroscopic dissection of cystectomy specimen.

- Using a small pair of scissors, open the ureters on both sides, beginning at the trigonal orifices (Figure 27-3B). Look for ureteral strictures and dilatations, and examine the mucosa for ulcerations or exophytic lesions. Document these findings in the gross dictation. Submit transverse sections of the ureters at regular intervals along their entire length.
- If a tumor is identified in the bladder, determine the depth of invasion. To do this, make full-thickness cuts through the tumor and bladder wall. If the tumor appears to infiltrate the muscular propria (detrusor muscle) of the bladder, record whether it invades the muscularis wall (inner half vs outer half), the perivesical fat, or the surrounding structures.

14. Submit sections for light microscopy. Tissue samples should include the lesion, the lesion with adjacent benign urothelial mucosa, ureteral orifices, urethral margin, any secondary lesions, and nonneoplastic mucosa.

- At least one section per centimeter of tumor to include:
  - Deepest of invasion
  - Full-thickness sections of the tumor and the bladder wall
  - Tumor and the adjacent uninvolved mucosa
  - Tumor and the deep soft tissue margin (if in close proximity)
- Any abnormal-appearing mucosa should be submitted.
  - Erythematous areas may indicate CIS
- Margins
  - Ureteral margins (if not submitted separately or for intraoperative frozen diagnosis), distal urethral margin
  - Deep soft tissue margin
- Ureter sections
  - Submit longitudinal sections of the ureter and the bladder mucosa interface.
  - If a long segment of the ureter is present, submit midportion sections.
- Uninvolved mucosa
  - Submit at least one section of each: the trigone, the dome, the anterior wall, the posterior wall, the left lateral wall, and the right lateral wall.
  - Submit more sections, particularly if the tumor is not grossly identified.

15. Look for, measure, and submit all lymph nodes in the perivesical fat.

16. Examination of the prostate gland is important for two reasons. First, if the bladder cancer directly infiltrates the prostate base, it is staged as pT4. In contrast, when urothelial CIS spreads along the prostate urethral mucosal with subsequent invasion into the prostate stroma, it is staged as pT2. The second reason is prostate adenocarcinoma may be found in the cystoprostatectomy specimens. Grossly identified lesion(s), prostatic urethra, and periurethral areas should be sampled.

- If no abnormal areas are identified, representative sections should be submitted to include:
  - Prostatic urethra with the surrounding prostatic parenchyma
  - Bilateral peripheral zones and central zones (3 to 4 sections each side)
  - Bilateral seminal vesicles (one section)

17. In females, the uterus, the fallopian tubes, the ovaries, uterus and the vaginal cuff should be examined for tumor involvement (refer to the respective chapters).

• Ink the vaginal cuff margin and submit en face.

• If no abnormal areas are identified, representative sections should be submitted to include:

- One section from each anterior and posterior endometrium
- One section from each ovary
- One section from each fallopian tube with the fimbriae
- One section from the vagina

The partial/subtotal cystectomy specimens contain portions of the bladder wall with four edges with mucosal and muscular surgical margins. Same principles for handling of a radical cystectomy should be used for these specimens. The margins should be inked and proximity to or involvement by the tumor should be noted. If the tumor is in close proximity to the margins, perpendicular sections should be taken.

In cases of urachal carcinoma for which partial cystectomy with excision of the urachal tract and umbilicus is performed, the margins of the urachal tract (ie, the soft tissue surrounding the urachus and the skin around the umbilicus) should be inked and submitted.

V. Gross description of cystoprostatectomy

Specimen A:

(A) Left distal ureter, margin inked - A 0.6 cm in length x 0.3 cm in diameter portion of tan-pink ureter with the margin inked by the surgeon. The margin is shaved and submitted en face in A1 for frozen and permanent section.

Frozen section diagnosis: No tumor present.

(B) Right distal ureter – A 1.2 x 0.8 cm portion of ureter orange and pink on the margin. The margin is shaved and submitted en face in B1 for frozen and permanent section.

Frozen section diagnosis: No tumor present.

(C) Bladder, prostate, and seminal vesicle: A radical cystoprostatectomy specimen consisting of a urinary bladder (11 x 10 x 3 cm, opened), prostate gland (4.5 x 4 x 3 cm), seminal vesicles (1.5 x 0.5 x 0.4 cm), and attached perivesical adipose tissue measuring overall (10 x 6 x 2 cm).

Located in the wall of the urinary bladder are two areas of ulceration. The first ulcerated lesion (2.0 x 1.5 cm) is present in the left posterior lateral wall, near the left ureteral orifice. The second ulcer (2.0 x 1.0 cm) is present in the right posterior lateral wall, near the right ureteral orifice. Each area of ulceration is erythematous with roughened surface. Serial sections through the ulcers show firm white-gray tissue, extending superficially into the lamina propria.

The remainder of the urinary bladder mucosa is edematous and unremarkable. Both ureteral orifice are probe patent. The prostate gland is nodular with nodules measuring up to 1.5 cm in greatest dimension. The seminal vesicles are grossly unremarkable.

Ink code

Posterior surface of urinary bladder and posterior surface of prostate: black

Left lateral surface of prostate and urinary bladder: red

Right lateral surface of prostate and urinary bladder: yellow

Anterior surface of prostate and urinary bladder: green

Section code

C1: Urethral margin, en face (if this margin was evaluated intra-operatively, no need to do again)

C2: Right prostatic apex, entirely submitted

C3: Left prostatic apex, entirely submitted

C4-7: First ulcerative area with the deepest invasion area, to include the adjacent benign mucosa and full thickness of bladder wall

C8-10: Second ulcerated area including deepest invasion area and adjacent benign mucosa and full thickness of bladder wall

C11: Anterior wall
C12: Dome
C13: Trigone
C14: Left ureteral orifices, including intramural portion
C15: Right ureteral orifices, including intramural portion
C16: Left seminal vesicle
C15: Right seminal vesicle
C16-17: Nodular area of prostate
C18: Prostate peripheral zone, more than one fragments
C19: Regional lymph nodes

Specimen D: Right pelvic lymph nodes- Two irregular fragments of fibrofatty tissue, measuring 3.5 x 2.0 x 1.5 cm in aggregate. Three possible lymph nodes are identified, the largest one is 1.5 cm.

Section code

D1-D3: One bisected lymph node each, entirely submitted

Specimen E: Left pelvic lymph nodes- Two irregular fragments of fibrofatty tissue, measuring 3.0 x 2.5 x 1.5 cm in aggregate. Four possible lymph nodes are identified, the largest one is 1.5 cm.

Section code

E1-E4: One bisected lymph node each, entirely submitted

VI. Common pathologic findings in cystoprostatectomy

The malignant tumors of the urinary tract, including the bladder, are classified on the basis of the 2016 World Health Organization classification.[1] Urothelial carcinoma is the most common type and accounts for 90% of the bladder cancer cases in industrialized countries; 70% to 80% are noninvasive or early invasive (Ta, Tis, or T1), 1% to 7% of the cases are squamous cell carcinoma, and 0.5% to 2% are primary adenocarcinoma of the bladder. Other epithelial lesions may be seen in resection specimen, including papilloma, urothelial dysplasia, cystitis cystica et glandularis, inflammation, squamous metaplasia, and reactive changes seen after chemotherapy or radiation therapy. Prostatic adenocarcinoma may be seen as an incidental finding, but it may be extensive and of advanced stage in some cases.

VII. Common potential staging pitfalls and solutions

It is essential to understand the staging criteria before grossing cystectomy specimens. The AJCC TNM system[2] is the well-accepted system to document the anatomic extent of the tumor in the specimens. T and N categories are derived from examining the resection and lymphadenectomy specimens. M category is assigned on the basis of clinical and pathologic examinations.

The depth of cancer invasion in the wall of the urinary bladder, a hollow organ, determines the stage of the cancer. The anatomic landmarks within the wall of the urinary bladder that are important for staging include muscularis mucosae, muscularis propria, and perivesical soft tissue. If there was presurgical treatment, cystectomy specimens should be staged as posttreatment using the “y” descriptor to indicate posttherapy. If there is no evidence of residual primary tumor, pT0 is assigned. pTa describes a noninvasive papillary carcinoma. If only urothelial CIS (flat tumor) is present, pTis is assigned.

The depth and extent of invasion into the subepithelial connective tissue/lamina propria/submucosa (pT1), muscularis propria (pT2), or beyond (pT3 or pT4) are the most important pathologic parameters obtained from cystectomy specimens. pT1 is to describe a tumor that invades lamina propria (subepithelial connective tissue). pT2 is used to stage a tumor that invades muscularis propria. pT2 tumor is substaged as pT2a (tumor invades superficial, or inner half of, muscularis propria) and pT2b (tumor invades deep, or outer half of, muscularis propria). If the tumor infiltrates through the muscularis propria to involve the perivesical soft tissue, pT3 is assigned, which is further divided into pT3a when the tumor invades the perivesical soft tissue microscopically and pT3b when the tumor invades the perivesical soft tissue macroscopically (extravesical mass). In patients who have a large bladder carcinoma that has invaded through the full thickness of the bladder wall to

secondarily involve the prostatic stroma (direct transmural invasion), a T4 stage should be assigned per urinary bladder staging. If urothelial carcinoma (in situ or invasive) spreads along the prostatic urethral mucosa and prostate glands and subsequently invades prostatic stroma (transurethral mucosal route), the urothelial carcinoma in the prostate should be staged as pT2 instead of pT4, and separate urinary bladder and prostatic urethral staging should be assigned. In urothelial carcinoma arising in a bladder diverticulum, no pT2 stage can be assigned because the detrusor muscle layer is absent in acquired diverticula.

For regional lymph node staging (pN), two pieces of information are critical: one is the number of lymph nodes involved by metastatic carcinoma, and the second is the anatomic location of the lymph nodes. If the nodes are in the true pelvis (including perivesical, obturator, internal and external iliac, or sacral areas), the number of positive nodes (one vs two or more) separates pN1 from pN2. A designation of pN3 means metastatic carcinoma is present in common iliac lymph nodes.

The M category is used to document distant metastasis. There is no MX. The absence of any clinical history or physical findings suggestive of metastases in a patient who has not undergone any imaging is sufficient to assign the clinical M0 category (cM0). There is no pM0. Biopsy or other pathologic information is required to assign the pM1 category. Patients with a negative biopsy of a suspected metastatic site are classified as clinical M0 (cM0). pM1 indicates metastatic disease confirmed by pathology. pM1a is used for metastasis that is limited to lymph nodes beyond the common iliac lymph nodes, whereas pM1b is for non–lymph node distant metastasis.

VII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, tumor site and size, histologic type, histologic grade, tumor extension, margins status, nodal involvement, and pathologic staging. The presence of associated epithelial lesions, tumor configuration, lymphovascular invasion, and additional pathologic findings may also be incorporated into the report.

Standard pathology report

Final pathologic diagnosis

Bladder, prostate, and seminal vesicles, radical cystoprostatectomy

- Invasive high-grade urothelial carcinoma, with focal micropapillary component, forming a 1.2-cm tumor mass in the trigone
- Tumor invades into the superficial muscularis propria
- All ureteral, urethral, and soft tissue resection margins negative for the tumor
- Urothelial CIS involving the right lateral wall of the bladder is present
- Lymphovascular invasion is present
- Prostate and bilateral seminal vesicles negative for tumor
- Three lymph nodes negative for metastatic carcinoma (0/3)
- Pathologic stage: pT2aN0

Synoptic report

Procedure: Radical cystoprostatectomy

Tumor site: Trigone

Tumor size: Greatest dimension: 1.2 cm; additional dimensions: 1.0 x 0.9 cm

Histologic type: Invasive urothelial carcinoma with focal micropapillary component

Histologic grade: High grade

Associated epithelial lesions: Urothelial CIS

Microscopic tumor extension: Tumor invades muscularis propria, inner half

Margins: Uninvolved by invasive carcinoma and CIS

Lymph-vascular invasion: Present

Regional lymph nodes

Number of lymph nodes examined: 3
Number of lymph nodes involved (any size): 0
Pathologic stage classification (pTNM, AJCC 8th ed)
Primary tumor (pT): pT2a
Regional lymph nodes (pN): pN0
Additional pathologic findings: Benign prostatic stromal and glandular hyperplasia
Comments: Blocks C5 and C6 may be used for future ancillary/molecular studies.

References

1. Humphrey PA, Moch H, Reuter VE, Ulbright TM, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs.* 4th ed. Geneva, Switzerland: WHO Press; 2016:77-133.
2. Bochner BH, Hansel DE, et al. Urinary bladder. In: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017:765-774.

28. Endometrium

Pei Hui, MD

I. Indications

This tumor-staging grossing protocol should be used for surgical-staging hysterectomy of endometrial carcinomas and carcinosarcoma (malignant mixed Müllerian tumor). The specimens may be derived from various formats of hysterectomy, including abdominal and vaginal approaches (open, laparoscopic, or robotic assisted). This protocol does not apply to uterine adenosarcoma (see hysterectomy protocol for uterine sarcomas) and lymphomas.[1,2]

II. What to expect in the hysterectomy specimens and typical macroscopic appearance

Single or multiple discrete polypoid masses or diffuse, exophytic endometrial growth are typical presentation of endometrial carcinomas (Figure 28-1). Rare cases may have an endophytic/infiltrative growth pattern with no obvious gross lesion. Necrosis and hemorrhage are common. Although gross presentation is generally not specific to any types of endometrial carcinoma, early lesions of endometrial serous carcinomas frequently involve an endometrial polyp. Background endometrial hyperplasia may show diffuse or polypoid endometrial thickening. Carcinosarcoma (malignant mixed Müllerian tumor) frequently presents as large polypoid intrauterine mass. Common coexisting benign conditions include leiomyoma, adenomyosis, and endometrial polyps.

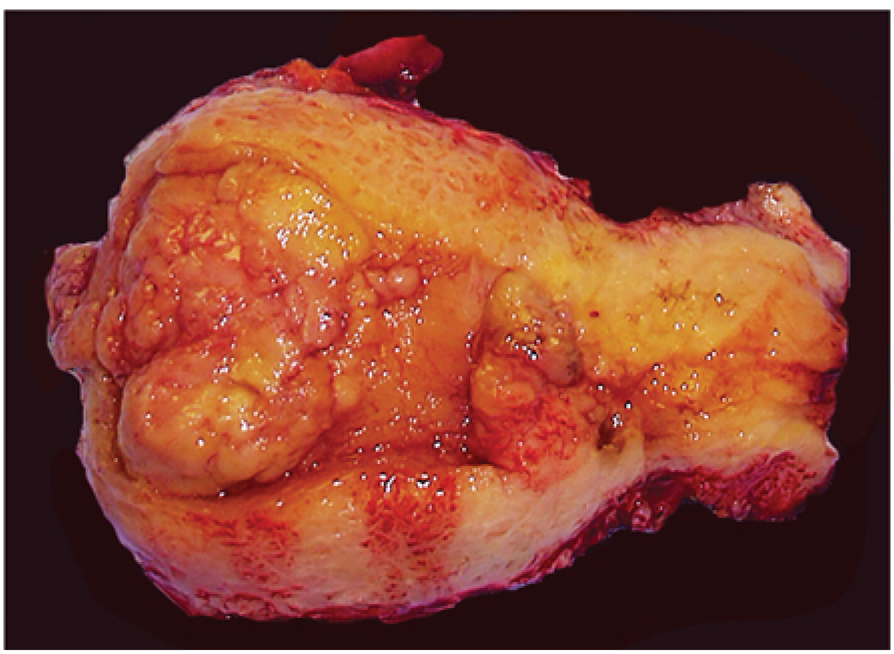

Figure 28-1. Gross presentation of endometrial adenocarcinoma. Multiple, discrete, polypoid masses involve endometrium in this example of well-differentiated endometrioid adenocarcinoma.

III. Dissection techniques: step-by-step description

1. Ideally, the uterus should be received intact and can be oriented to identify the anterior and posterior aspects. The presence of deeper peritoneal reflection indicates the posterior uterine surface. If the adnexa are attached, the ovary is located posterior to the fallopian tube. It is important to document if the uterus is received open or morcellated.

2. The entire specimen is weighed, and the three dimensions of the uterus are measured to include the length, width between cornua, and anterior-to-posterior thickness in centimeters. Measure the diameter and the length of the cervix, and examine the cervical os for patency, noting its diameter.

3. Uterine serosal surface is inspected for color, texture, and presence of any adhesions, nodules, or cystic lesions. Note any gross lesions at the cervical os.

4. The uterus is opened coronally into anterior and posterior halves (Figure 28-2). To achieve this, a long thumb dressing forceps is inserted through the cervical canal to the fundus of the uterus, followed by sectioning using a sharp blade to open the cervical canal and the endometrial cavity using the thumb dressing forceps as a guide.

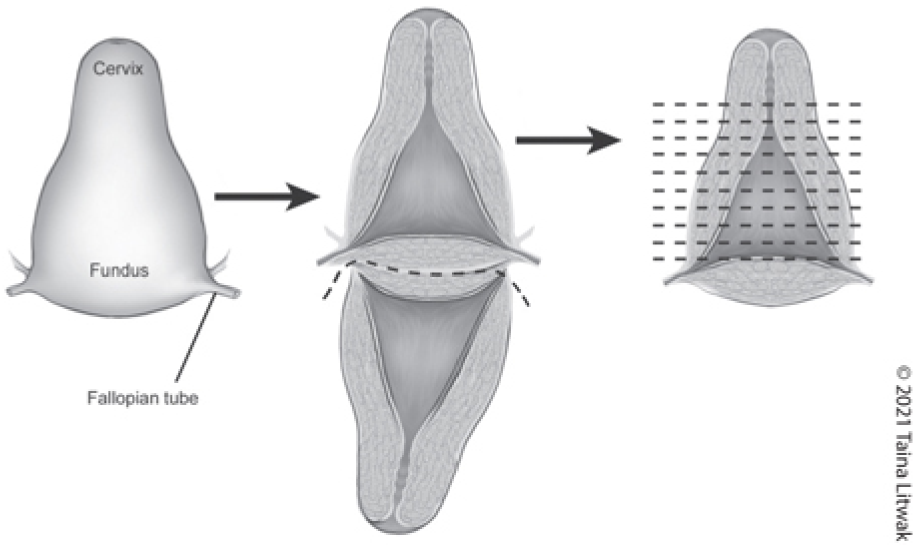

Figure 28-2. Grossing hysterectomy specimen is typically achieved by coronal sectioning of uterus into anterior and posterior halves. In addition, each half of the uterus is serially sectioned.

5. The length of cervical canal is measured, and cervical mucosa and stroma are inspected for lesions. The shape and size of the endometrial cavity are documented. Describe the location (fundus, entire cavity, or lower uterine segment) and the size of the gross lesion, if any, and presence or absence of gross tumor extension to the lower uterine segment and/or endocervix. The background endometrium is described with regard to color and thickness, the texture of the endometrium is noted, and the presence of mucosal lesions and any distortion of the endometrial cavity by intramural or submucosal lesions are noted.

6. Anterior and posterior endomyometrium are serial sectioned. The cut surface of myometrium is inspected for color and texture and maximal thickness. The depth of carcinoma invasion is estimated as percentage of the thickness of myometrium (Figure 28-3). Trabeculation and nodularity (adenomyosis) and discrete, tan-white, rubbery nodules with whorled appearance (leiomyomata) are noted. The location (subserosal, intramural, submucosal, transmural) and any variation in the cut surface (necrosis, calcification, and hemorrhage) should be noted.

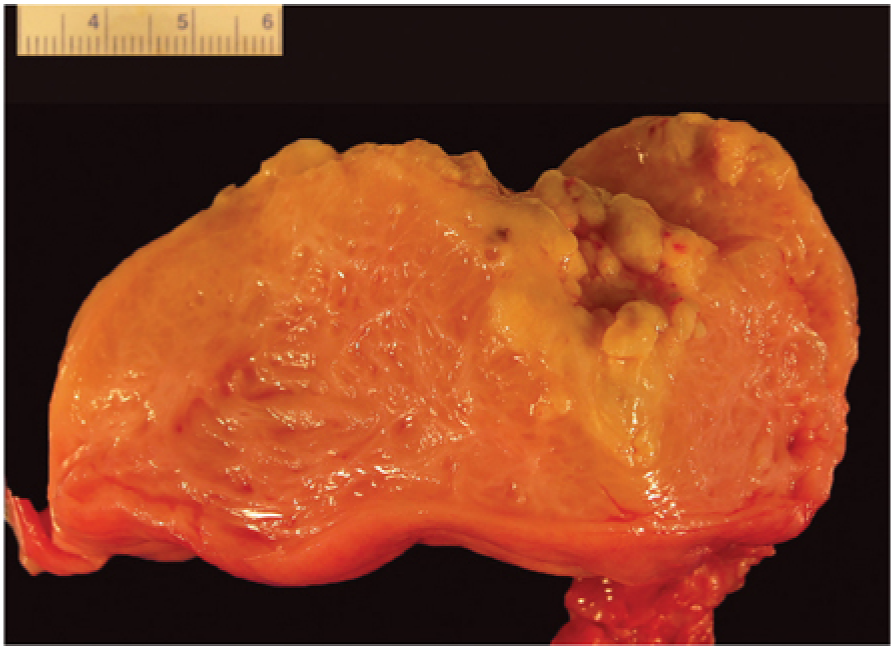

Figure 28-3. Gross estimation of the depth of tumor invasion as percentage of the thickness of myometrium.

The following tissue sections should be embedded:

- Sections of anterior (12 o'clock) and posterior (6 o'clock) cervix, including transformation zone and endocervix, should be submitted.
- Submit at least four full-thickness sections to show the maximum depth of myometrial tumor invasion.
- Submit three or four additional sections of endometrium (not full thickness, multiple sections per cassette). If the uterine wall is too thick to fit in one cassette, a cross-section should be bisected and submitted in two adjacent cassettes and so noted in the gross description. Sections containing transitional areas (cancer and noncancerous areas) are helpful for measurement of myometrial invasion. Submit sections of any additional lesions, polyps, and leiomyomata. One section of anterior and one section of posterior lower uterine segment contiguous with upper endocervix are important for evaluation of cervical tumor extension. Separate standard anterior and posterior cervical sections are submitted. Representative sections of left and right parametrial soft tissue are also submitted, if present. Entire bilateral adnexae are submitted.

IV. Grossing description using paragraph system

Received fresh, labeled with the patient's name and "uterus, ovaries and fallopian tubes" is total hysterectomy and bilateral salpingo-oophorectomy specimen, including uterus and its attached bilateral adnexae. The specimen weighs 65 grams. The corpus uterus measures 12.0 (cornua to cornua) x 5.5 (length) x 3.0 cm (anterior to posterior thickness). The uterine serosa is tan-pink and smooth. The whitish tan, glistening ectocervix (3.0 x 2.8 cm) displays an eccentric 0.5-cm slit-like os. Sectioning reveals a 1.5 cm in length and 0.6 cm in diameter endocervical canal with tan-pink, slightly corrugated endocervical canal with multiple thin, smooth-walled Nabothian cysts.

The endometrial cavity (4.5 cm in length, 2.2 cm cornu to cornu) is distorted by a tan-pink polypoid mass (3.5 x 3.0 cm) at the anterior endometrium. The mass is friable, tan to yellow on cut surface, with areas of hemorrhage and necrosis. The background endometrium is diffusely thickened with an average thickness of 4 mm. The tan-red, trabeculated myometrium measures up to 3.5 cm thick.

Cut surface of myometrium demonstrates extension of the endometrial lesion to involve 60% of anterior myometrium. Several myometrial nodules are seen, ranging from 0.5 to 1.5 cm in size, with rubbery, tan, cut surface. The attached tan-yellow, lobulated ovaries (1.5 x 1.0 x 0.4 cm on the right and 1.6 x 0.8 x 0.3 cm on the

left) display a tan-yellow, smooth stroma upon sectioning. The attached tan-red fimbriated fallopian tubes (both measuring approximately 3.5 x 0.5 cm) display a stellate, pinpoint lumen upon sectioning.

Representative sections are submitted in 25 cassettes as follows:

Cassette 1: Anterior cervix (12 o'clock)

Cassette 2: Posterior cervix (6 o'clock)

Cassette 3: Anterior lower uterine segment with extension to upper cervix

Cassette 4: Posterior lower uterine segment with extension to upper cervix

Cassettes 5-9: Anterior endomyometrial mass, including full thickness of myometrium to serosa

Cassettes 10-12: Remaining anterior endometrium

Cassettes 13-16: Posterior endomyometrium, including serosa

Cassettes 17-19: Sections of myometrial nodules

Cassettes 20-22: Sections of entire right ovary and fallopian tube

Cassettes 23-25: Sections of entire left ovary and fallopian tube

V. Common staging pitfalls and solutions

1. Myometrial invasion

- Myometrial invasion is recorded as percentage of myoinvasion over the total thickness of the myometrium where the deepest myoinvasion is found (Figure 28-4).
- Depth of myoinvasion is measured from the deepest invasion to the junction of endomyometrium, which may be identified by the presence of normal nonneoplastic glands on a better-oriented endomyometrial section.
- Adenomyosis involved by carcinoma is separated from true myoinvasion by the presence of nonneoplastic glands nearby or at the forefront of the tumor nests with compression (Figure 28-5). Absence of adenomyosis foci nearby or in other sections of endomyometrium indicates true myoinvasion, even in the absence of stromal response. It should be emphasized that CD10 is not a helpful marker in such setting.

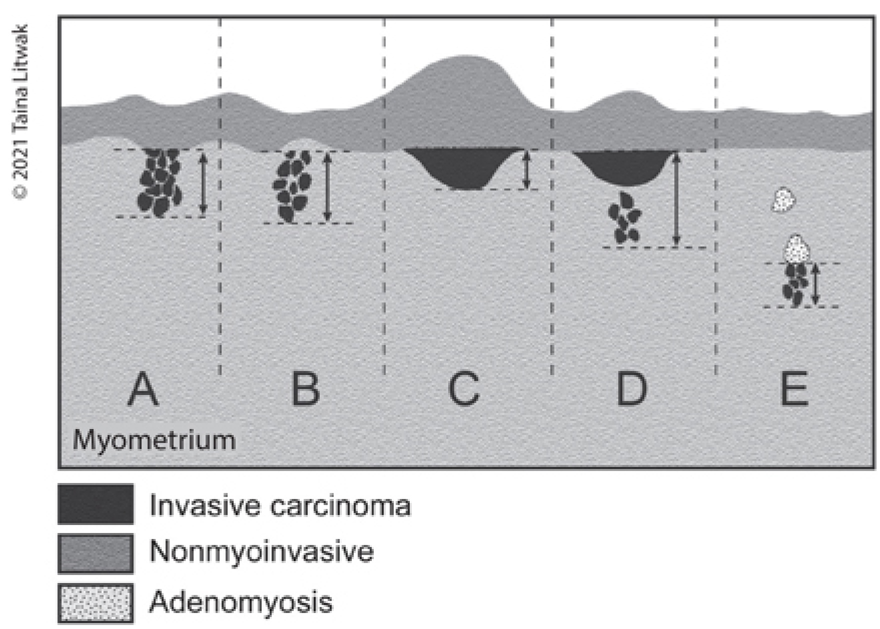

Figure 28-4. Diagram of microscopic measurement of myometrial invasion.

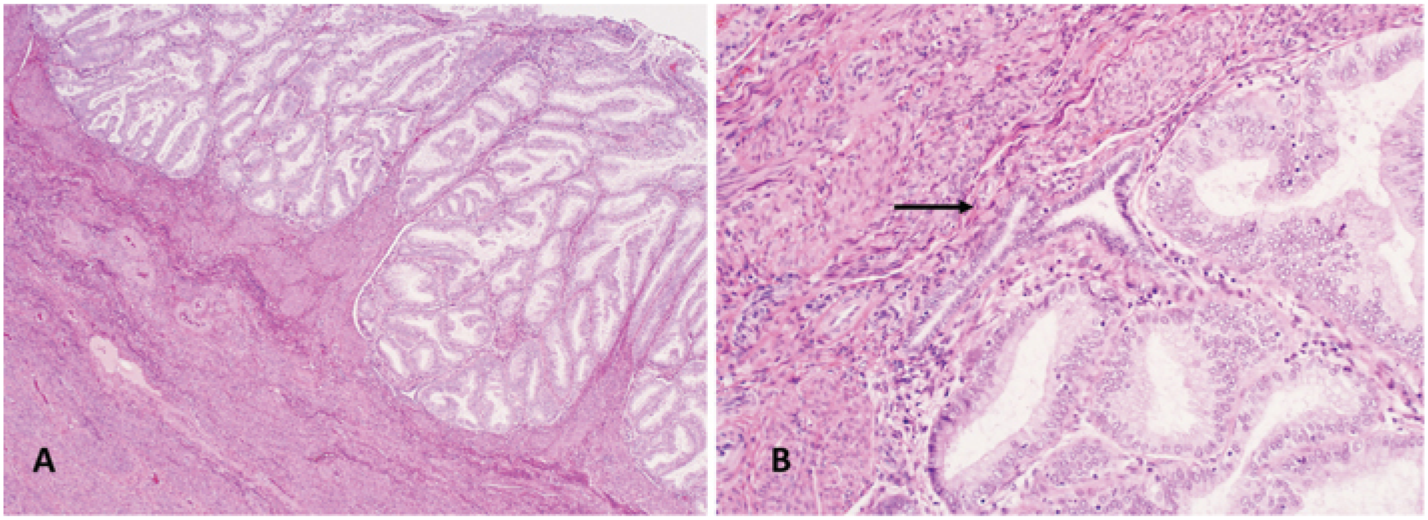

Figure 28-5. Pseudomyometrial invasion is recognized by the presence of benign endometrial glands at the front of carcinoma nests (low-power view [A] and high-power view B]).

2. When myoinvasion arises in deep-seated adenomyosis foci, particularly arising in the outer half of the myometrium, the staging depth of myoinvasion is controversial. It is reasonable to measure the distance of the invasion point to the overlying endomyometrial junction. Another approach is to measure the distance from invasive front to the involved adenomyosis focus as the depth of invasion (Figure 28-4), which is divided by the total myometrium thickness to deduce the percentage of myoinvasion.

3. Cervical involvement

Only cervical stromal involvement is considered stage II disease. Histologic features of stromal invasion include desmoplastic stromal response around tumor glands, haphazard infiltrative growth, or confluent growth (Figure 28-6). Extension of endometrial carcinoma onto cervical mucosal surface or glandular epithelium does not upstage the tumor.

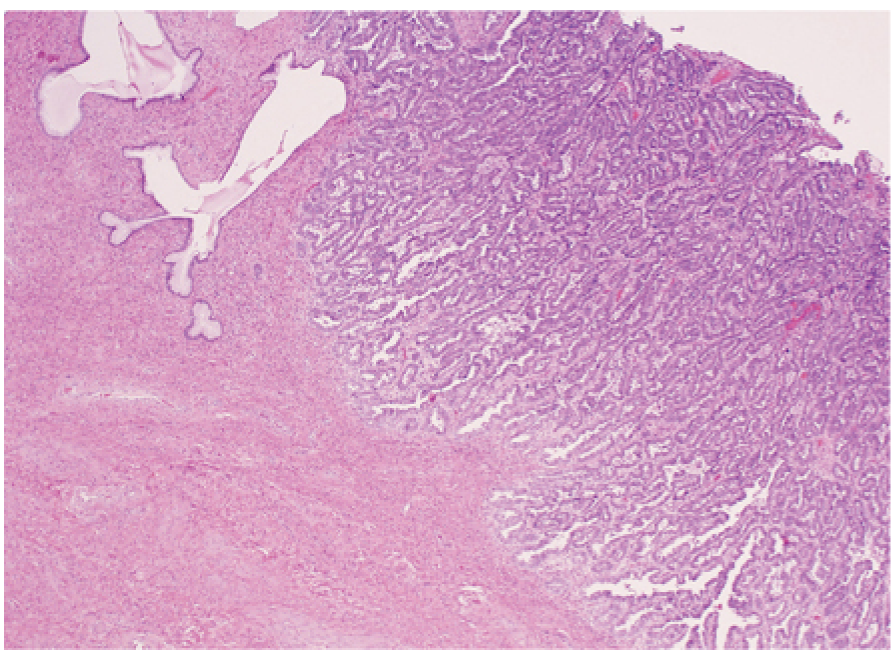

Figure 28-6. Cervical stromal involvement by endometrial serous carcinoma is recognized by confluent growth of carcinoma glands in this example.

4. Lower uterine segment involvement

Endometrial carcinoma in patients with Lynch syndrome more likely presents at the lower uterine segment.

5. Parametrial invasion

In case of radical hysterectomy, the parametrial surgical margin is inked, and the entire parametrial soft tissue should be embedded.

6. Fallopian tube involvement

Free-floating tumor tissue fragments become more common with the increasing use of robotic-assisted hysterectomy and is considered artifact and should not upstage the tumor (Figure 28-7). An explanatory note may be necessary to document the finding.

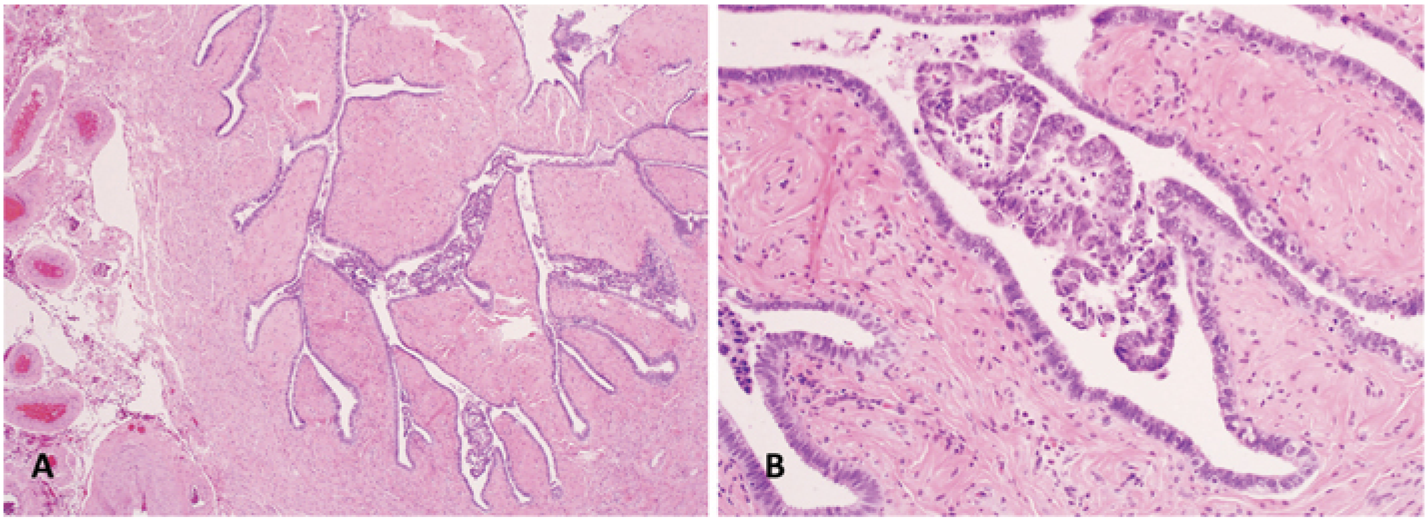

Figure 28-7. Free-floating tumor tissue fragment within the fallopian tube lumen is considered artifact, particularly in a robotic-assisted hysterectomy (low-power view [A] and high-power view [B]).

When focus of mucosal serous carcinoma involving fallopian tube is found along with endometrial serous carcinoma, the primary site should be considered endometrial if the tubal focus is smaller than the uterine tumor volume.

7. Lymphovascular invasion

The presence of lymphovascular invasion (LVI) is clinically relevant in terms of likelihood of nodal metastasis.

LVI outside of the uterus, including the cervix and adnexa, has not been confirmed to have prognostic implication and does not upstage the tumor by the International Federation of Gynecology and Obstetrics (FIGO) staging system.

Pseudo-LVI as a result of mechanical displacement often presents as tumor fragments in larger-caliber thick-walled vessels at the outer half of the myometrium, in the absence of small-vessel involvement of the inner half of the myometrium.

8. Grading

Tumor grading is not applicable to serous, clear cell, undifferentiated, dedifferentiated, high-grade neuroendocrine carcinomas and malignant mixed Müllerian tumor. Mixed carcinoma is a high-grade cancer by World Health Organization definition.

When FIGO architectural grade is 1 or 2, the presence of grade 3 nuclei in more than 50% of tumor cells upgrades the tumor by one level.

9. Mixed carcinoma

The definition of mixed carcinoma entails two or more carcinoma histologic types, one of which must be type II carcinomas (serous or clear cell) and in at least 5% of the total tumor volume.

10. Carcinosarcoma

The definition of carcinosarcoma entails the presence of both epithelial (carcinomatous) and mesenchymal (sarcomatous) malignant components in the tumor. The two components are distinct and sharply demarcated

histologically, although focal merging can be seen. The epithelial component is high grade in most cases, but the mesenchymal component is almost always high-grade sarcoma types of either homologous or heterologous nature.

11. Surgical margins

For endometrial carcinoma staging, true surgical margins include distal cervix/vaginal cuff and parametrium, if present and involved by the tumor.

12. Peritoneal washing of ascites cytology

Positive peritoneal cytology does not upstage the tumor but is reported in a separate statement.

13. Disrupted or morcellated uterine specimens

The integrity of uterine specimen must be documented and reported.

14. Lymph node dissection

There is no established standard regarding the optimal number of lymph nodes reported from pelvic or paraaortic dissections. A median number of 10 to 12 nodes from bilateral pelvic dissection and 5 to 6 nodes from paraaortic dissection are acceptable at some major institutions.

Sentinel lymph node evaluation has been increasingly used recently for staging hysterectomy of endometrial cancers; however, there has been no consensus as to how to process these lymph nodes—ultrastaging. Among various ultrastaging proposals, one approach at the author's institution is to evaluate deeper (50 μm deep), consecutive sections of the lymph node by hematoxylin-eosin (H&E) and by cytokeratin immunostain when the initial H&E section shows no evidence of metastasis (Figure 28-8).

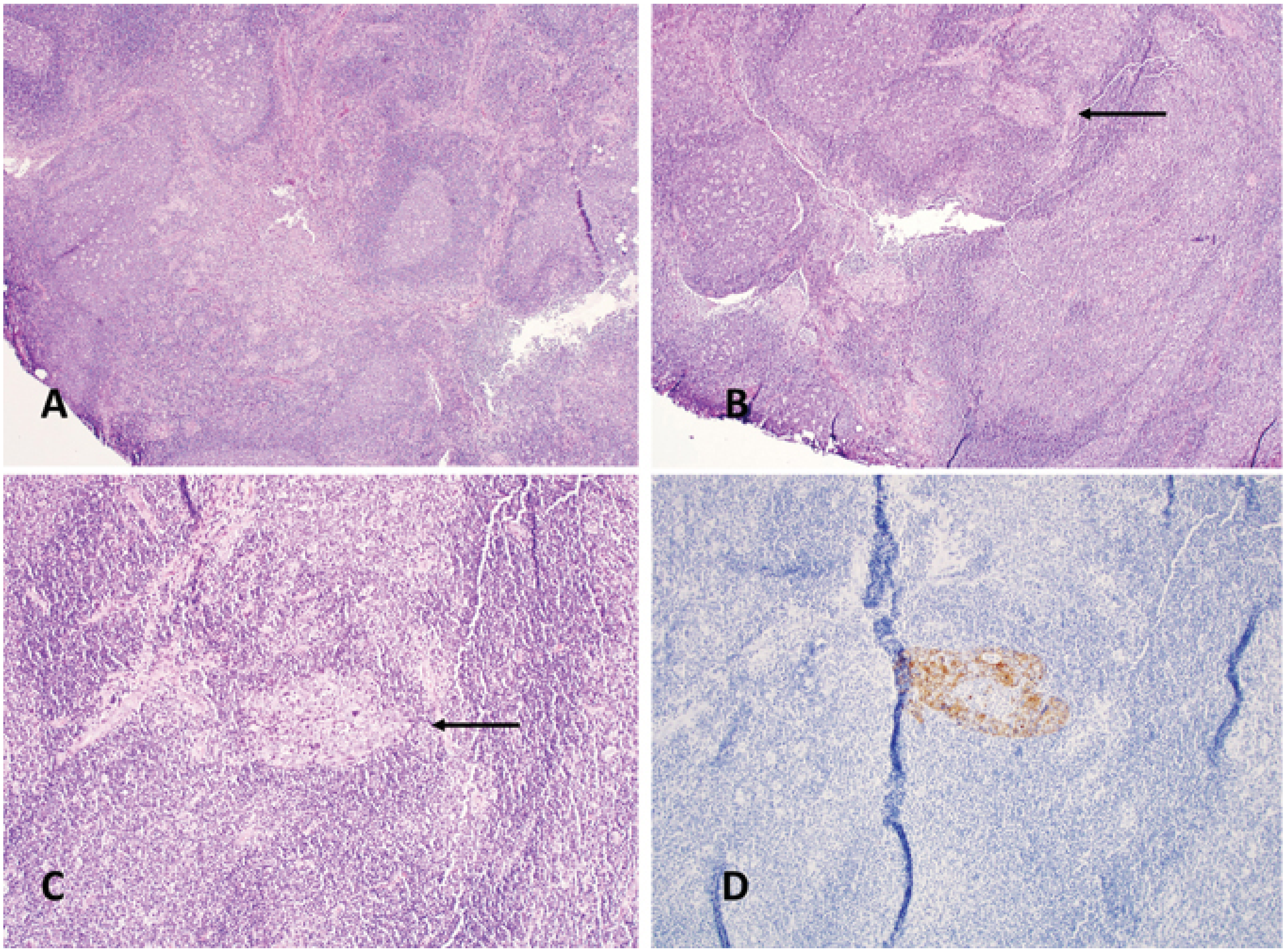

Figure 28-8. Sentinel lymph node evaluation by deeper section of hematoxylin-eosin (H&E) and by cytokeratin immunostain reveals the presence of microscopic metastasis after the initial H&E section is negative. Initial H&E section shows no evidence of metastasis (A). Micrometastasis is revealed by deep level section (B, low power; C, high power) and confirmed by cytokeratin AE1/3 immunostain (D).

Separating microscopic lymph node metastasis from benign endosalpingiosis can be difficult. Careful comparative histologic and cytologic evaluation is essential, and, when necessary, appropriate immunohistochemistry may be important (Figure 28-9).

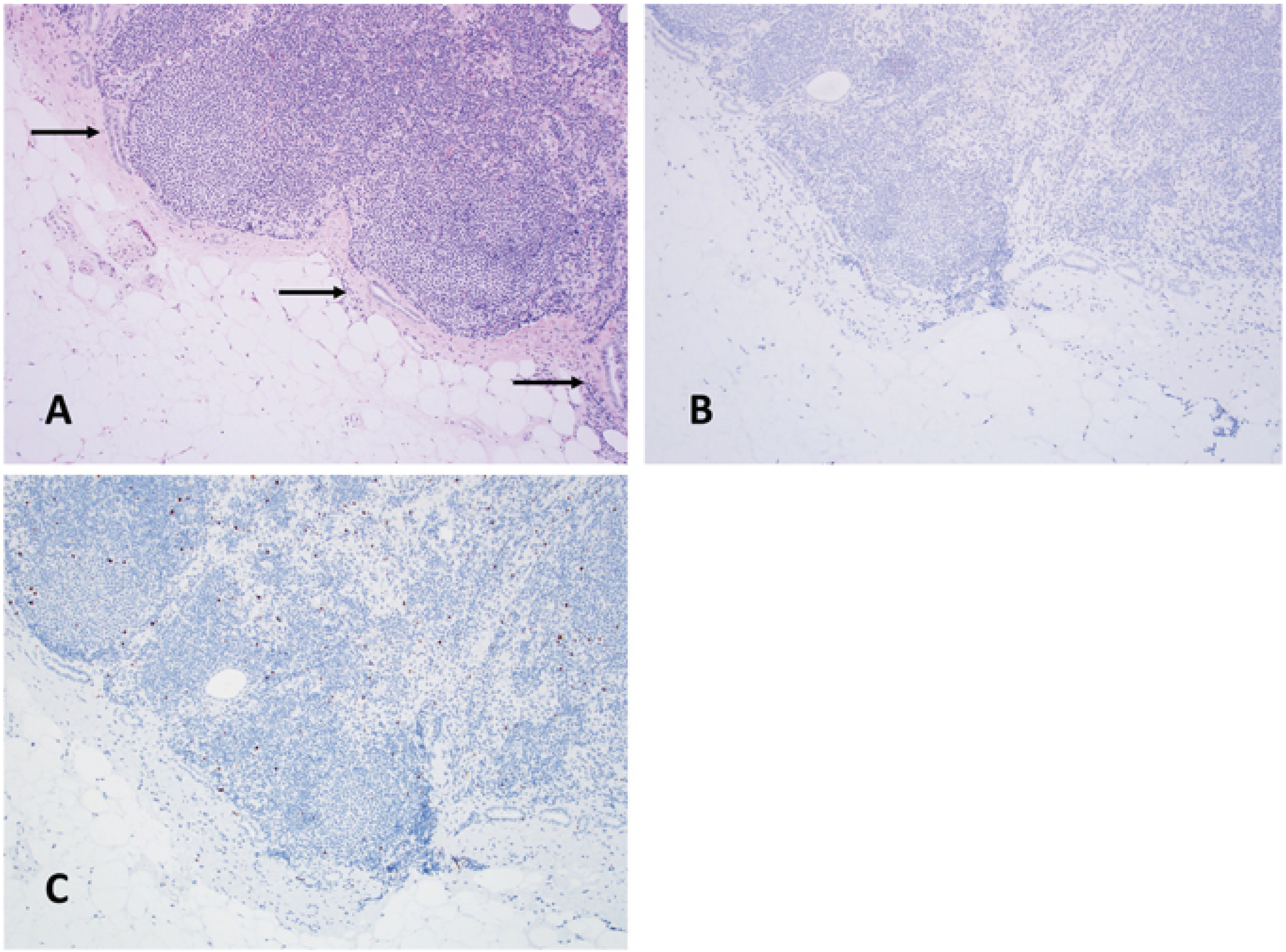

Figure 28-9. Pelvic lymph node with endosalpingiosis can be correctly diagnosed by careful histologic and immunohistochemical comparison with primary endometrial serous cancer. A. Hematoxylin-eosin section showing endosalpingiosis at several lymph node subcapsular regions. Absence of p53 immunostain (B) and low level of Ki-67 labeling (C) in endosalpingiosis glands.

15. In case of biopsy-confirmed tumor that is not resected for any reason, if the highest stage tumor sites or lymph node involvement can be confirmed microscopically, pathologic staging should be reported without the removal of the primary tumor.

VI. What to include in the pathology report

- Surgical procedures
- Hysterectomy types
- Specimen integrity
- Tumor size and location
- Histologic diagnosis and grading
- Depth of myometrial invasion
- Lower uterine segment involvement
- Cervical involvement
- Uterine serosa involvement
- LVI
- Other peritoneal organs/tissue involvement, including ovaries, fallopian tubes, omentum, pelvic peritoneum
- Surgical margins (cervical and parametrial surgical margins)
- Pelvic lymph node status

- Regional lymph nodes are strictly defined to include lymph nodes designated as pelvic, parametrial, obturator, internal or external or common iliac, sacral, presacral, and para- or periaortic lymph nodes. Involvement of lymph nodes of inguinal region, omentum, or mesentery is considered M1.
- Number of lymph nodes identified
- Number of lymph nodes with metastatic tumor
- Number of sentinel lymph nodes

• Size of metastatic tumor in lymph node (isolated tumor cells, ≤0.2 mm; micrometastasis, >0.2 to 2 mm; macrometastasis, >2 mm)
• Distant metastases, including abdominal lymph nodes (excluding paraaortic lymph nodes), inguinal lymph nodes, organs beyond abdomen, intraperitoneal organs excluding regional lymph nodes, vagina, pelvic serosa and adnexa
• Peritoneal fluid/ascites cytology
• American Joint Committee on Cancer (AJCC) tumor staging/FIGO staging

Samples for final diagnosis and synoptic report

Final diagnosis

Uterus, ovaries, fallopian tubes, omentum and pelvic lymph nodes; total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node dissections:

• Endometrial adenocarcinoma, endometrioid type and FIGO grade 2
• Myometrial invasion of >50%
• Tumor involving cervical stroma
• Micrometastasis to two paraaortic lymph nodes
• AJCC tumor staging (AJCC 8th ed): pT2N2miM0; FIGO stage: IIIC[1]
• See synoptic report for details

Synoptic report

• Specimen: Uterus, ovaries, fallopian tubes, omentum, and pelvic lymph nodes
• Procedures: Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node dissections
• Specimen integrity: Intact uterus
• Tumor site: Anterior endometrium
• Tumor size: 3.5 cm
• Histologic type: Endometrioid carcinoma, NOS
• Histologic grade: FIGO grade 2
• Myometrial invasion: Present (54%)
  - Depth of invasion: 7 mm
  - Myometrial thickness: 13 mm
• Adenomyosis: Present and involved by carcinoma
• Uterine serosa: Not involved by tumor
• Lower uterine segment involvement: Present
• Cervical involvement: Both stroma and mucosa
• Peritoneal/ascitic fluid: Positive for carcinoma
• LVI: Present
• Ovaries: Not involved by tumor
• Fallopian tubes: Not involved by tumor
• Omentum: Not involved by tumor
• Distal cervical and parametrial soft tissue margins: Not involved
• Regional lymph nodes
  - Total number of lymph nodes examined: 26
  - Total number of lymph nodes involved: 2
  - Total number of pelvic lymph nodes: 20

- Total number of pelvic lymph nodes involved: 0
  - Total number of paraaortic lymph nodes: 6
  - Total number of paraaortic lymph nodes involved: 2 (mi)
- Other findings: Endometrial hyperplasia with atypia, leiomyomas, and left ovarian fibroma
- Pathologic stage (pTNM, AJCC 8th ed)
  - Primary tumor (pT): pT2
  - Regional lymph nodes (pN): pN2mi
  - Distant metastasis: pM0
  - FIGO stage: IIIC

References

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29. Ovary, Fallopian Tube, and Peritoneum

Natalia Buza, MD

Part I. Salpingo-oophorectomy

I. Applications and indications

Surgical staging of borderline and malignant ovarian tumors, fallopian tube carcinomas, and primary peritoneal carcinomas typically includes bilateral salpingo-oophorectomy with hysterectomy, omentectomy, regional lymphadenectomy, and often additional peritoneal biopsies. Salpingo-oophorectomy is also performed as part of the surgical staging procedure for endometrial and cervical carcinomas and as a prophylactic procedure in patients with genetic predisposition for ovarian and/or tubal carcinomas.

Discussion in this chapter is limited to primary epithelial, germ cell, and sex cord–stromal malignancies; lymphomas, sarcomas, and peritoneal mesotheliomas are not included.

II. Gross specimen processing and documentation Gross description

The gross description should start with the specimen weight, followed by three-dimensional measurements of the ovary and at least two measurements (length and diameter) of the fallopian tube. Describe the ovarian surface and make note of the capsule integrity (intact versus ruptured/disrupted), any surface irregularities, and adhesions (Figure 29-1). Inking the ovarian surface—at least partially for larger tumors, in the area of irregularity—is helpful when it comes to microscopic evaluation of surface involvement (Figure 29-2). Describe the fallopian tube serosal surface and presence of any tubo-ovarian adhesions or grossly apparent mass lesions. Take gross photographs before and after sectioning.

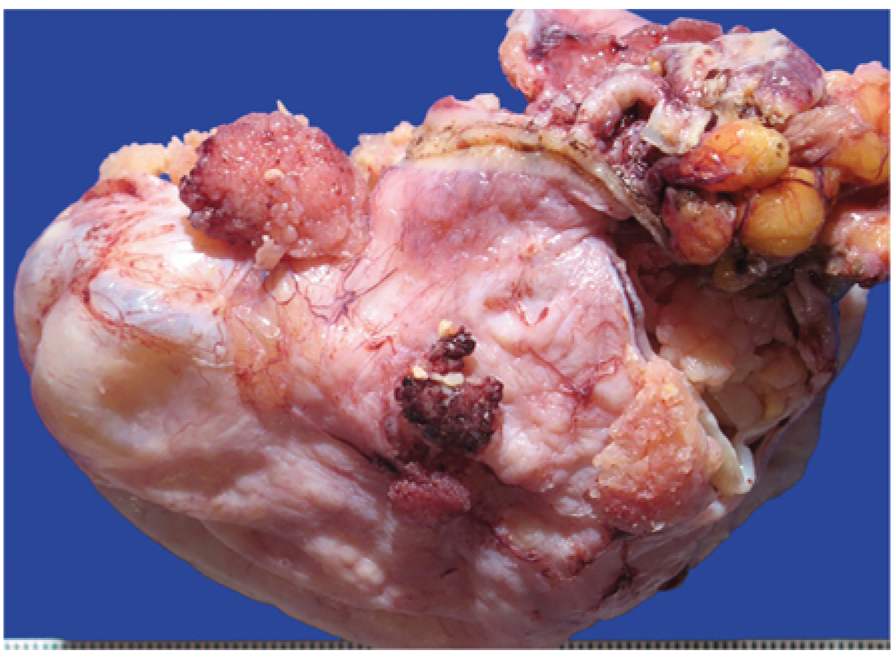

Figure 29-1. High-grade serous carcinoma with grossly apparent ovarian surface involvement.

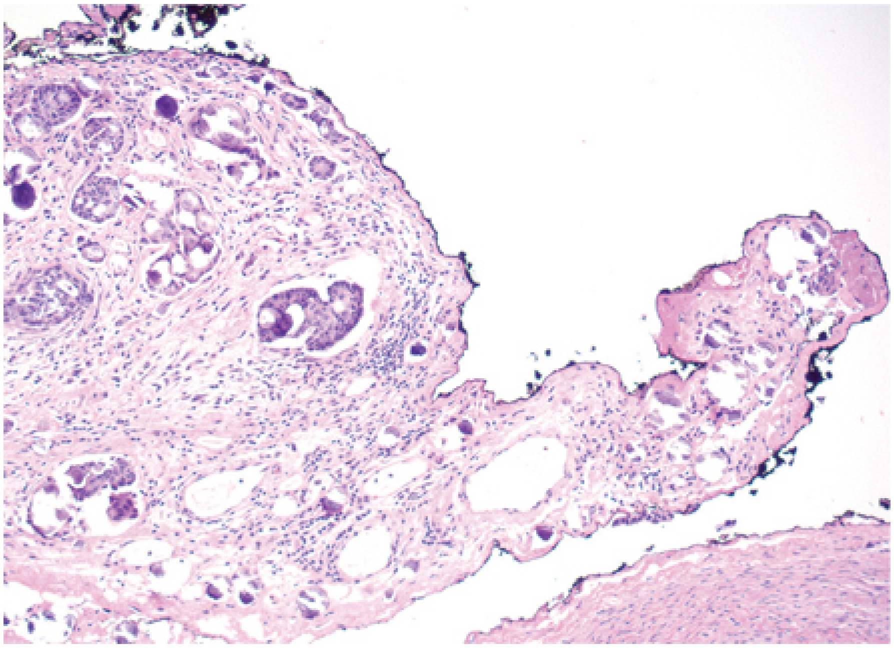

Figure 29-2. Ovarian low-grade serous carcinoma. Black ink on the ovarian surface helps confirm surface involvement microscopically.

Gross sectioning, sections submitted

For predominantly solid ovarian masses, serially section the entire ovary, and measure the size of any discrete masses or make a note if the ovarian parenchyma is diffusely replaced by tumor. Describe the consistency, color, and nodularity of the mass, and indicate if there are any gross areas of necrosis or hemorrhage. If the tumor is predominantly cystic, the largest cyst can be opened first, followed by description of cyst contents and cyst lining, and serial sectioning and description of the cyst wall and the number of cysts—unilocular versus multilocular. As a general rule of thumb, one section per centimeter of tumor should be submitted, including sections representing the ovarian surface, focusing on areas of irregularity and adhesions. For tumors larger than 10 cm, the number of sections can be limited to 10 on the initial submission. In predominantly cystic tumors, sampling should focus on areas of intraluminal papillary and/or solid growth. The number of sections should be adjusted on the basis of the tumor histologic type and heterogeneity of gross appearance. For example, mucinous ovarian tumors often require more extensive sampling due to their frequent microscopic heterogeneity.

The fimbriated end of the fallopian tube should be sectioned parallel to the fimbria, the middle and proximal segments sectioned perpendicular to the lumen, and the entire fallopian tube submitted (see part IV for "sectioning and extensively examining the fimbriated end" [SEE-FIM] protocol).

Sample gross description

Received fresh, labeled with the patient's name, medical record number and "left tube and ovary" is a 365-gram salpingo-oophorectomy specimen consisting of a 13 x 12 x 6 cm ovary and an attached 7 cm in length and 0.7 cm in diameter fallopian tube. The ovarian surface is intact and shows two areas of tan-pink, firm, irregular nodularity, measuring 1.3 cm and 1.7 cm in largest dimensions. The ovarian surface is inked blue. The ovary is serially sectioned to reveal a multiloculated, cystic cut surface replacing the entire ovarian parenchyma. The cyst contents are clear and serous, and the lining shows numerous papillary excrescences and a few tan-pink, firm, solid nodules. Gross photographs are taken before and after sectioning. The fallopian tube is sectioned to reveal grossly unremarkable fimbria and a pinpoint lumen. Representative sections are submitted as follows: cassettes #1-10: ovarian mass (including surface nodularity in cassettes #8-#10); cassettes #11-13: fallopian tube, entirely submitted (fimbriated end in cassette #11).

III. Common pathologic findings

There is a broad spectrum of primary ovarian malignancies with a large number of well-defined histopathologic entities that may be identified in salpingo-oophorectomy specimens. However, in the routine pathology practice, ovarian epithelial tumors predominate, with high-grade serous carcinoma (HGSC) being the most commonly encountered ovarian malignancy by far. Other types of serous (low-grade serous carcinoma, serous borderline tumor), mucinous, endometrioid, and clear cell epithelial neoplasms are less common. Only 2% to 3% of ovarian malignant tumors are of germ cell origin, which are most often seen in patients younger than 30 years. Malignant sex cord–stromal tumors may also occur, comprising approximately 1% to 2% of all primary ovarian malignancies.

In addition, ovaries are not uncommon metastatic sites for carcinomas arising in the gastrointestinal tract, breast, and in other gynecologic organs (ie, endometrium and cervix). It is crucial for patient management and also for staging purposes to accurately distinguish between primary versus metastatic carcinomas of the ovary. However, a detailed discussion of the differential diagnostic features and ancillary studies is beyond the scope of this publication.

IV. Potential staging pitfalls and solutions

Staging of ovarian and fallopian tube tumors is based on the local extent of tumor: ovarian surface involvement, fallopian tube (for ovarian primaries) or ovarian (for tubal primaries) involvement, extension to other pelvic sites or extrapelvic peritoneum (eg, omentum, capsule of liver or spleen), and pelvic and/or retroperitoneal lymph node involvement. For details on evaluation of omentum and regional lymph nodes, see parts II and III in this chapter.

The current (2018) American Joint Committee on Cancer (AJCC) staging manual[1] applies a unified staging system for ovarian and fallopian tube malignancies and primary peritoneal carcinomas, regardless of the primary tumor site, although it still requires primary tumor site assignment. This may be challenging in HGSC because there are no uniform guidelines in this regard, and significant interobserver variability probably exists among pathologists. Different approaches have been proposed in the literature: the traditional approach has been primary site assignment based on the dominant tumor mass and tumor distribution—for example, a large ovarian HGSC with microscopic foci of tubal mucosal and/or peritoneal involvement would be considered an ovarian primary with secondary tubal and/or peritoneal spread. More recently, with emerging evidence supporting the role of tubal precursor/early lesions in the pathogenesis of HGSC, fallopian tube has been proposed as the primary site in the presence of one of the following findings: serous tubal intraepithelial carcinoma (STIC), invasive HGSC in the tubal mucosa (with or without STIC), or fallopian tube partially or entirely incorporated into a tubo-ovarian mass.[2-4] Fallopian tube involvement on the serosal surface alone, without tubal mucosal involvement, is not sufficient to designate the tumor as tubal primary. HGSCs with predominant peritoneal/omental involvement and normal-sized ovaries with only surface involvement or stromal involvement of less than 5 mm would be classified as primary peritoneal carcinomas in the absence of STIC or tubal mucosal invasive HGSC.

In some cases, the tumor stage may depend on the primary site assignment—for example, cases with both STIC in the fallopian tube and HGSC with stromal invasion in the ovary: if the tumor is considered an ovarian primary, it would be stage IA, whereas if the STIC is considered to be the primary site with secondary ovarian involvement, it would be stage IIA. In difficult cases with multifocal involvement, discussion with the clinical team is often helpful to ensure optimal patient management.

STIC only, even without stromal invasion, has the capacity for exfoliation and transperitoneal metastatic spread; therefore, it should be staged as stage I (IA if unilateral, IB if bilateral, and IC3 if the peritoneal washings are positive) (Figure 29-3). Endometrial serous carcinoma may also spread to the fallopian tube and colonize the mucosal epithelial surface, mimicking a primary STIC. Generous sampling of the endometrium, particularly any endometrial polyps, is helpful to rule out an endometrial primary. WT1 immunohistochemistry may also be useful in this setting: tubal HGSC and STIC are typically WT1 positive, whereas most endometrial serous carcinomas are WT1 negative.[5] However, WT1 positivity may be seen in approximately 30% of the latter, presenting a potential diagnostic pitfall.

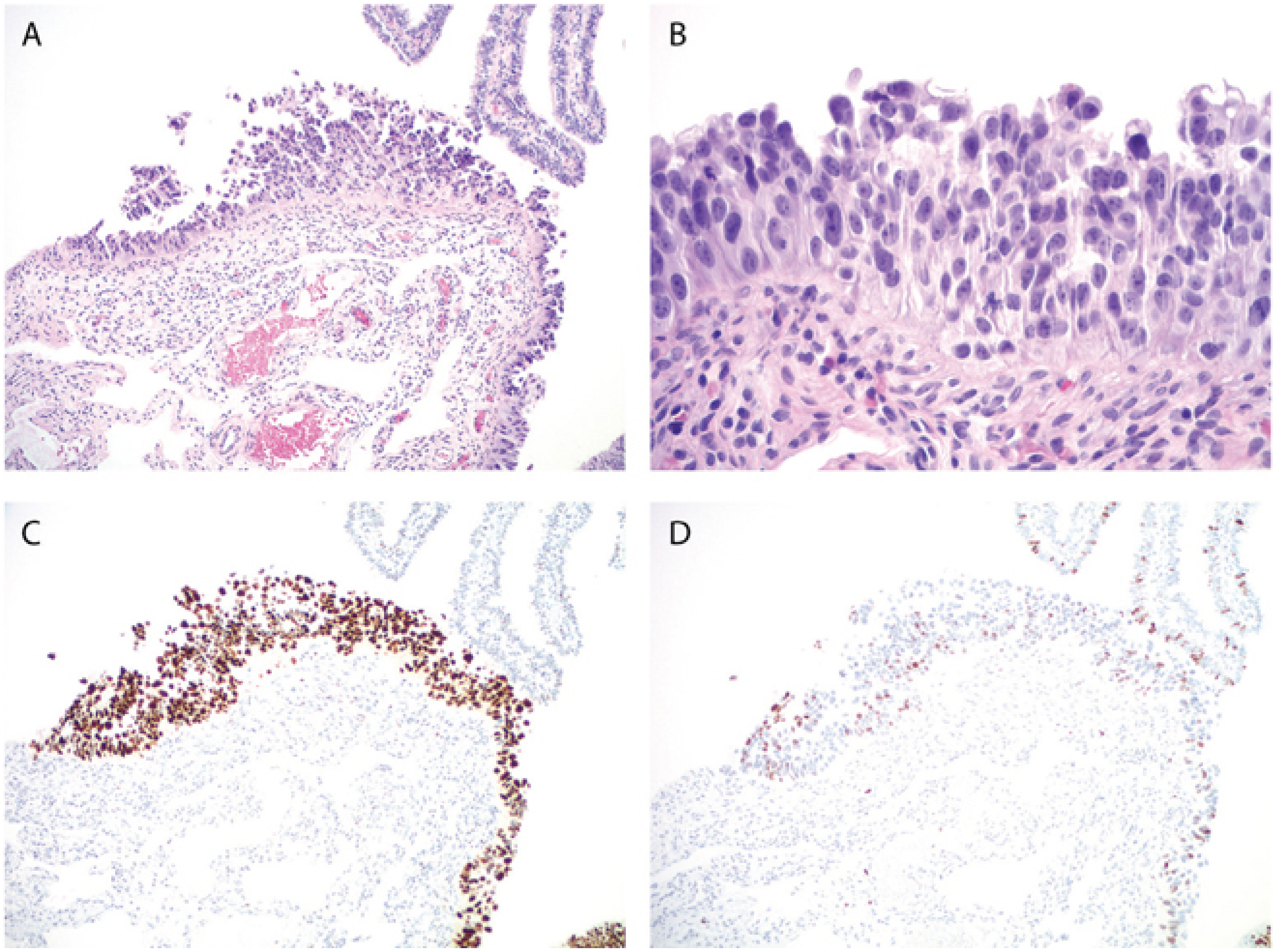

Figure 29-3. Serous tubal intraepithelial carcinoma. A, B. The tumor cells show proliferation with loss of polarity, hyperchromasia, marked nuclear atypia, and mitotic activity. C. p53 immunostain is strongly and diffusely positive. D. Ki-67 immunostain shows an increased proliferation index. Note the contrast with normal fallopian tube epithelium in the right upper corner.

Ovarian surface involvement may be difficult to assess with certainty, especially if the sections taken from the surface are not designated as such and the surface was not inked and described accurately at the time of grossing. Following the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system for ovary, the 2018 AJCC staging subdivided stage IC into three prognostic groups: stage IC1, intraoperative rupture ("surgical spill"); stage IC2, capsule rupture before surgery or tumor on ovarian/tubal surface; and stage IC3, malignant cells in ascites or peritoneal washings. Pathologic evaluation of the integrity of ovarian surface/capsule may be limited if the tumor was removed laparoscopically and was ruptured or fragmented within a specimen bag by the surgeon. In such cases, the specimen integrity may be listed as intact, with an explanatory note referring to the surgeon's operative report.

Splenectomy and resection of a portion of the liver may also be performed as part of the tumor debulking/staging surgery for ovarian/tubal/primary peritoneal carcinoma. It is crucial to distinguish between capsular and parenchymal tumor involvement in these cases. Tumors involving the splenic or liver capsule are stage IIIB or IIIC, depending on the size of the metastatic focus, whereas involvement of liver and/or spleen parenchyma should be staged as stage IVB. In addition, transmural bowel involvement is now also classified as stage IVB in the current AJCC staging manual. Bowel involvement that is less than transmural should be staged on the basis of its location, namely, below or above the pelvic brim: intrapelvic bowel involvement would be staged as pT2b, and if the involved bowel segment is outside the pelvis, the stage would depend on the size of metastatic foci (pT3a, pT3b, or pT3c). Discussion with the surgeon may be helpful to determine the intrapelvic versus extrapelvic location of the involved bowel segment in equivocal cases.

Peritoneal surface involvement of the diaphragm or abdominal wall is considered pT3; however, if the tumor extends to the skeletal muscle of the diaphragm or abdominal wall soft tissues (eg, periumbilical soft tissue and skin metastasis), it should be designated as M1b, stage IVB.

For staging pitfalls and solutions regarding the omentum and regional lymph nodes in ovarian/tubal/primary peritoneal cancer, see parts II and III.

V. Essential components of the final pathology report

The final pathology report of a salpingo-oophorectomy must include the following:

1. Site and procedure performed
2. Tumor histologic type
3. Tumor grade, if applicable, based on histologic type
4. Tumor size
5. Ovarian surface involvement
6. Fallopian tube involvement: Specify if mucosal or serosal
   a. Presence of tubal intraepithelial carcinoma (if applicable)
7. Other specified sites of involvement
   a. Uterine serosa
   b. Pelvic peritoneum
   c. Omentum and/or other extrapelvic peritoneal samples
   d. Liver and/or spleen: Specify if capsule or parenchyma
   e. Bowel: Specify the extent of bowel wall involvement and whether it is transmural
8. Lymph node involvement
   a. Total number of lymph nodes examined
   b. Site(s) and number of metastatic lymph nodes
   c. Size of largest metastatic focus
9. Results of peritoneal washing cytology

Samples for final diagnosis and synoptic report

Final diagnosis

Uterus, bilateral ovaries and fallopian tubes, omentum, and bilateral pelvic and periaortic lymph nodes; total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node dissections

- High-grade serous carcinoma of the right ovary, 6.5 cm
- Ovarian surface is involved by carcinoma
- Left ovary and bilateral fallopian tubes are without significant abnormalities
- Uterus
  - Atrophic endometrium
  - Cervix, myometrium, and serosa without significant abnormalities
- Omentum: Involved by carcinoma (microscopic foci only)
- Bilateral pelvic and periaortic lymph nodes: negative for carcinoma
- AJCC stage (8th ed): pT3a N0, stage IIIA2

Synoptic report

Specimen: Uterus, bilateral ovaries and fallopian tubes, omentum, and bilateral pelvic and periaortic lymph nodes

Procedure: Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node dissections

Tumor type: High-grade serous carcinoma

Primary tumor site: Right ovary

Tumor size: 6.5 cm

Specimen integrity: Intact

Ovarian surface: Involved by tumor

Right fallopian tube: Not involved

Left ovary: Not involved
Left fallopian tube: Not involved
Uterus: Not involved
Omentum: Involved by carcinoma, microscopic foci only
Total number of lymph nodes examined: 18
Total number of lymph nodes involved: 0
Left pelvic lymph nodes examined: 6
Left pelvic lymph nodes involved: 0
Right pelvic lymph nodes examined: 6
Right pelvic lymph nodes involved: 0
Left periaortic lymph nodes examined: 3
Left periaortic lymph nodes involved: 0
Right periaortic lymph nodes examined: 3
Right periaortic lymph nodes involved: 0
Pelvic washing cytology: Positive for malignant cells
Pathologic staging (pTNM): pT3a N0 Mx, at least stage IIIA2

Part II. Omentectomy

I. Gross specimen processing and documentation Gross description

The gross description of omentectomy should start with a three-dimensional measurement of the specimen, followed by description and measurement of any apparent surface irregularities, adhesions, or nodules. If multiple surface nodules are present, indicate the number (few, several, numerous, etc) and size range of nodules. Describe if diffuse gross omental involvement is present (ie, "omental caking"). Take gross photographs.

Gross sectioning, sections submitted

Section the specimen at 1-cm intervals. Describe the cut surfaces and note the absence or presence of any nodules or mass lesions. Carefully measure the size of the largest mass lesion. Note if diffuse involvement is apparent on cut sections.

In the absence of a gross lesion, submit 10 random sections in five cassettes: two sections/cassette. If nodules are present, submit representative sections from different nodules within the omentum, in up to five cassettes.

Sample gross description

Received fresh, labeled with the patient's name, medical record number and "omentum" is a 25- x 16- x 3.8-cm portion of lobulated yellow adipose tissue, with a smooth glistening surface. Serial sectioning reveals two firm, tan-white, focally hemorrhagic, irregularly shaped masses measuring 6 x 5 x 3 cm and 2.5 x 1 x 1 cm. Gross photographs are taken. Representative sections from the two mass lesions are submitted as follows: cassettes #1-3: larger mass; cassette #4: smaller mass.

II. Common pathologic findings

The omentum is a common metastatic site from ovarian and tubal primaries. The extent of omental involvement may range from small microscopic foci to diffuse tumor infiltration, practically replacing the entire omentum (omental caking). In addition, common reactive and benign conditions may be encountered in omentectomy specimens, for example, reactive papillary mesothelial proliferation, endosalpingiosis, endometriosis, and peritoneal inclusion cysts.

III. Potential staging pitfalls and solutions

Omental involvement has a significant impact on prognosis and tumor stage of ovarian/tubal tumors; hence, accurate microscopic assessment of omental lesions is critical. Several benign or reactive conditions may mimic

omental involvement by borderline or malignant ovarian tumors. Reactive mesothelial proliferation is frequently encountered in association with ovarian tumors and may show various morphologic patterns: nested, trabeculated, papillary, or tubular. Lack of significant nuclear atypia, low mitotic activity, abundant eosinophilic cytoplasm and “cobblestone” appearance are helpful features to rule out a malignant process. Immunohistochemical stains—particularly PAX8—may also be useful in this setting, although it should be noted that PAX8 immunoreactivity is not specific to ovarian/Müllerian origin and may also be expressed in benign and malignant mesothelial proliferations.[6]

Endosalpingiosis—benign glands lined by tubal-type epithelium—is often seen in patients with serous tumors (serous borderline tumor [SBT] or low-grade serous carcinoma). It lacks significant epithelial proliferation, architectural complexity, and cytological atypia and should not be overinterpreted as an implant of ovarian SBT. Omental/peritoneal involvement by ovarian SBT traditionally has been classified into two categories: noninvasive and invasive implants. Invasive implants have also been termed low-grade serous carcinoma, as they represent the most important adverse prognostic factor in SBT.[7,8] The type of implant, however, does not alter the AJCC tumor stage.

Occasionally, peritoneal or omental sections show dense adhesions with psammoma bodies only, without accompanying epithelial tumor cells (Figure 29-4). Adhesions and calcifications by themselves do not justify increasing the tumor stage. Deeper level sections and/or submission of additional tissue blocks may be helpful in identifying adjacent tumor cells.

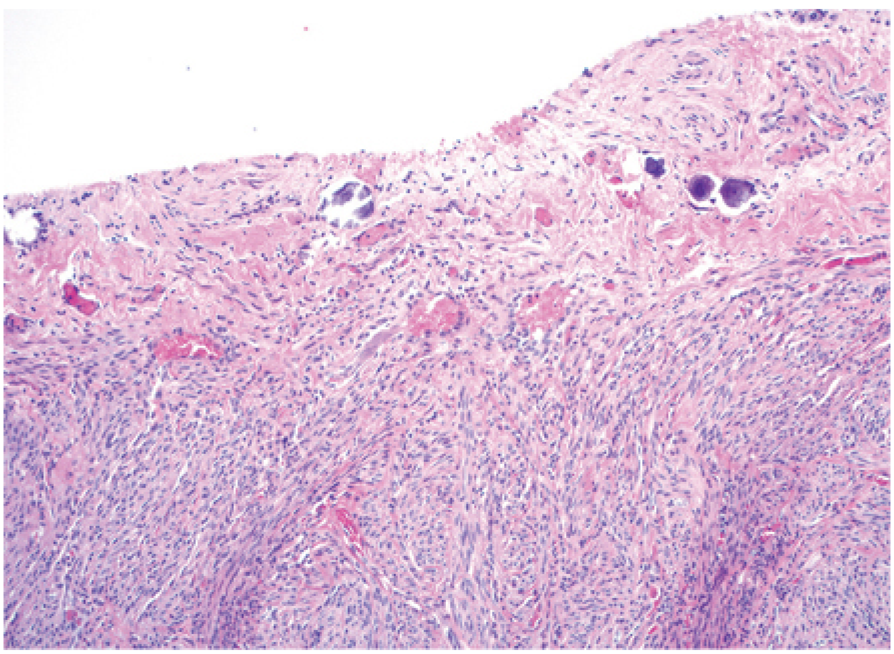

Figure 29-4. Uterine serosa with fibrous adhesions and psammomatous calcifications only, without associated tumor cells. The ovaries showed low-grade serous carcinoma.

Well-differentiated papillary mesothelioma—a small, benign proliferation of bland mesothelial cells—may also mimic an SBT implant (Figure 29-5). Lack of significant nuclear atypia, low mitotic activity, and lack of stromal invasion are characteristic and help the distinction.

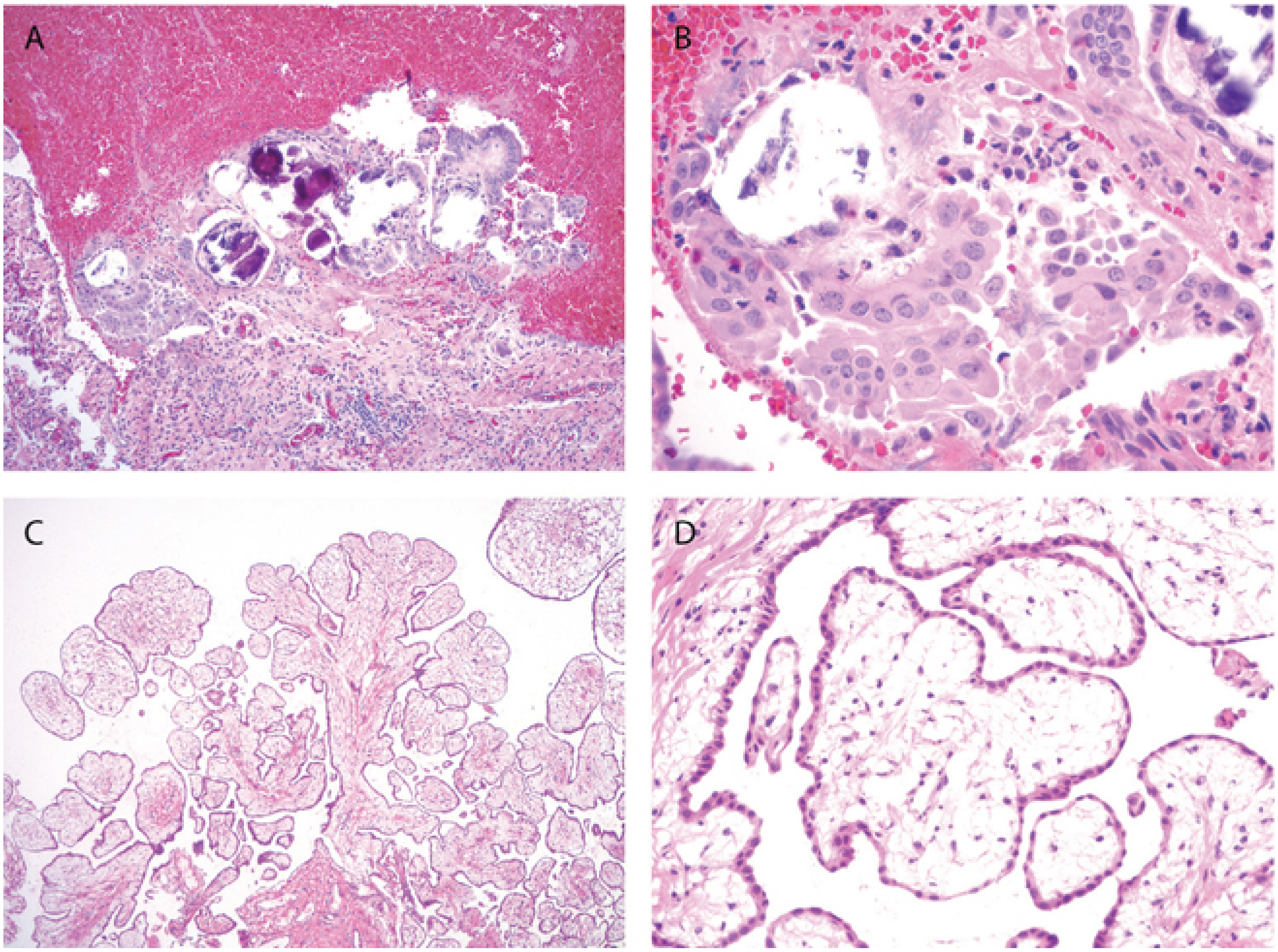

Figure 29-5. A, B. Noninvasive implant of serous borderline tumor shows papillary architecture with epithelial proliferation, tufting, and mild nuclear atypia. Ciliated cells and psammomatous calcifications are common. C, D. Well-differentiated papillary mesothelioma shows fibrovascular cores lined by a single layer of bland mesothelial cells without significant proliferative activity or tufting (frozen section).

Pseudomyxoma peritonei—peritoneal involvement by abundant, brown-yellow, mucinous material—is very rarely associated with primary ovarian tumors and most often arises from a low-grade appendiceal mucinous neoplasm. Thorough evaluation of the appendix is warranted for accurate identification of the site of origin. Immunohistochemical stains—CK7, CK20, CDX2, PAX8, and ER—may be helpful in this setting; however, there is significant overlap in the immunohistochemical profile of primary and metastatic ovarian mucinous tumors.

Part III. Regional (pelvic and periaortic) lymph node dissection

I. Gross specimen processing and documentation Gross description

Start the gross description with the three-dimensional measurement of specimen. The individual lymph nodes need to be dissected carefully from the adipose tissue. Describe the number and size range of dissected lymph nodes. Describe the cut surfaces of lymph nodes and comment on the presence and size of any firm white foci grossly suspicious for metastatic disease. Make a note if multiple matted, grossly involved lymph nodes are present. Measure the overall size of the matted lymph nodes.

Gross sectioning, sections submitted

Small (<0.5 cm) lymph nodes may be submitted without sectioning; larger lymph nodes need to be serially sectioned. Grossly negative lymph nodes need to be entirely submitted, whereas representative sections are sufficient for grossly extensively involved and/or matted lymph nodes. Be sure to submit the largest gross

metastatic focus to help staging distinction between N1a (metastasis up to 10 mm) and N1b (more than 10-mm metastatic focus).

If multiple lymph nodes are present, submit each serially sectioned larger lymph node in its own cassette or multiple cassettes. Multiple, smaller, intact lymph nodes can be submitted in the same cassette. The number of lymph nodes in each cassette needs to be clearly designated.

If no lymph nodes are grossly identified, submit representative sections of adipose tissue.

Sample gross description

Received fresh, labeled with the patient's name, medical record number and "left pelvic lymph nodes" is a 5.3- x 4.5- x 1.5-cm aggregate of adipose tissue, containing seven tan-pink rubbery lymph nodes, ranging from 0.4 cm to 2.3 cm in largest dimension. The three largest lymph nodes are serially sectioned. Cut sections of the largest lymph node show a 0.9-cm, ill-defined, tan-firm area. The smaller lymph nodes are grossly unremarkable. The lymph nodes are entirely submitted as follows: cassettes #1-2: largest, grossly suspicious lymph node, serially sectioned; cassettes #3-4: one serially sectioned lymph node in each cassette; cassette #5: two intact small lymph nodes.

II. Common pathologic findings

Metastatic spread to regional lymph nodes is not uncommon in ovarian epithelial malignancies. The size of metastatic focus should be carefully measured microscopically, as it has a significant impact on tumor stage in the absence of extrapelvic peritoneal involvement: metastatic foci measuring not more than 0.2 mm should be considered isolated tumor cells and designated as "N0(i+)." If the size of metastatic focus measures more than 0.2 mm but not more than 10 mm, the lymph node status is N1a, whereas lymph node metastases greater than 10 mm are considered N1b.

III. Potential staging pitfalls and solutions

Regional lymph nodes for ovarian/tubal/primary peritoneal cancer include pelvic (external iliac, internal iliac, common iliac, obturator, sacral, presacral) and periaortic/paraaortic lymph nodes. Extraabdominal (eg, inguinal, axillary, and supraclavicular) lymph node involvement should be considered distant metastasis (M1b, stage IVB).

Omental and mesenteric lymph nodes are not specified in the FIGO or AJCC staging manuals. One approach would consider these as regional lymph nodes for staging purposes, although it is arguable whether tumors with negative omental and/or mesenteric lymph nodes only—without pelvic and/or periaortic lymph node dissection—would be adequately staged as N0 or would be perhaps best to be designated as Nx.

Extracapsular extension has no impact on the lymph node stage. Tumor cells within a lymphovascular space outside of the lymph node capsule should not be designated as N1.

Endosalpingiosis—benign glands lined by tubal-type epithelium—is often seen within the lymph node capsule or parenchyma in patients with serous tumors (serous borderline tumor [SBT] or low-grade serous carcinoma) (Figure 29-6). It lacks significant epithelial proliferation, architectural complexity, and cytological atypia and should not be misinterpreted as a lymph node metastasis.

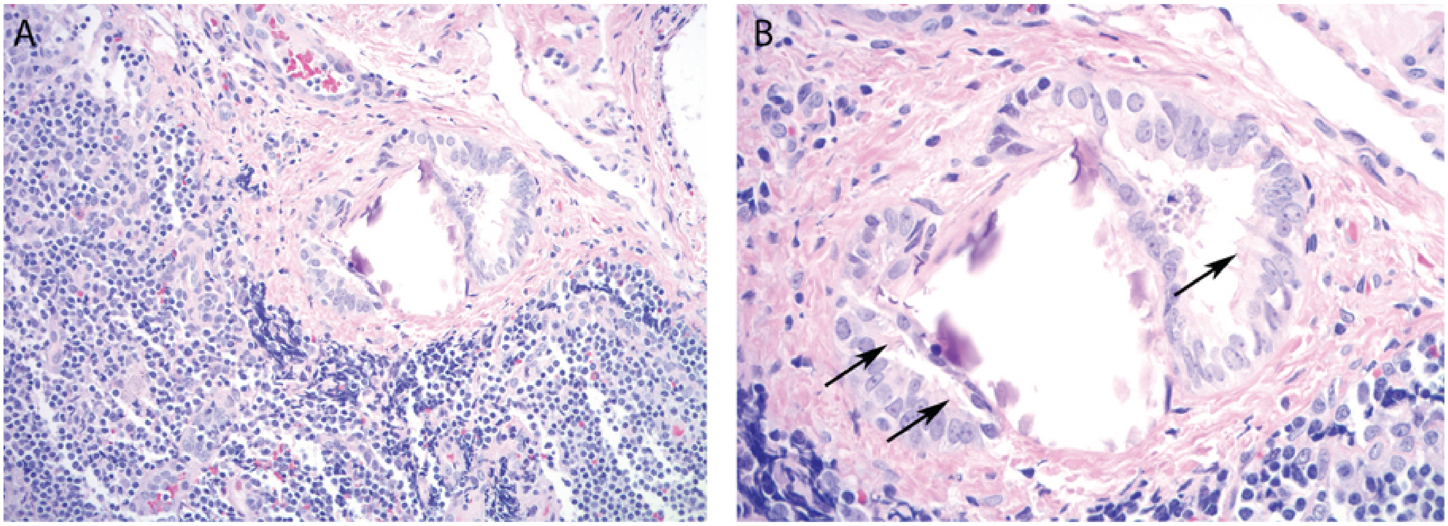

Figure 29-6. Endosalpingiosis in a lymph node. Note the intracapsular location (A), presence of cilia (B, arrows) and lack of significant nuclear atypia.

Part IV. Risk-reducing salpingo-oophorectomy

I. Applications and indications

The incidence of occult malignancy among *BRCA1/2* mutation carriers—including both in situ (STIC) and invasive (HGSC) carcinomas—in risk-reducing salpingo-oophorectomy (RRSO) specimens ranges between 5% and 10% in most published studies.[9-12] The goal of pathology evaluation is to identify any malignant tumors or precursor lesions with careful gross examination and thorough sampling to allow for complete surgical staging and early therapeutic interventions in these patients.

II. Gross specimen processing and documentation Gross description

In recent years, the "sectioning and extensively examining the fimbriated end" (SEE-FIM) grossing protocol of RRSO specimens in *BRCA1/2* patients has significantly improved the detection of early tubal neoplasms.[9,13] The SEE-FIM protocol should also be followed in other high-risk patients: those with strong family history of breast and/or ovarian cancer and/or with personal history of breast cancer.

The gross description should start with the specimen weight, followed by three-dimensional measurements of the ovary and at least two measurements (length and diameter) of the fallopian tube. Describe the ovarian surface and make note of the capsule integrity, any surface irregularities, and adhesions. If an ovarian mass lesion or surface irregularity is observed, the ovarian surface should be inked. Describe the fallopian tube serosal surface and presence of any tuboovarian adhesions or grossly apparent mass lesions. Take gross photographs before and after sectioning.

Gross sectioning, sections submitted

Per the SEE-FIM protocol, the specimen should be fixed in formalin for at least 1 to 2 hours before sectioning. The distal 2-cm portion of the fallopian tube with the fimbriated end should be amputated and sectioned into four sections (at approximately 2-mm intervals) parallel to the fimbria. The remainder of the tube should be sectioned at 2- to 3-mm intervals, perpendicular to the lumen (Figure 29-7). The ovaries should also be sectioned at 2- to 3-mm intervals. The entire fallopian tube and ovary should be submitted for histologic examination.

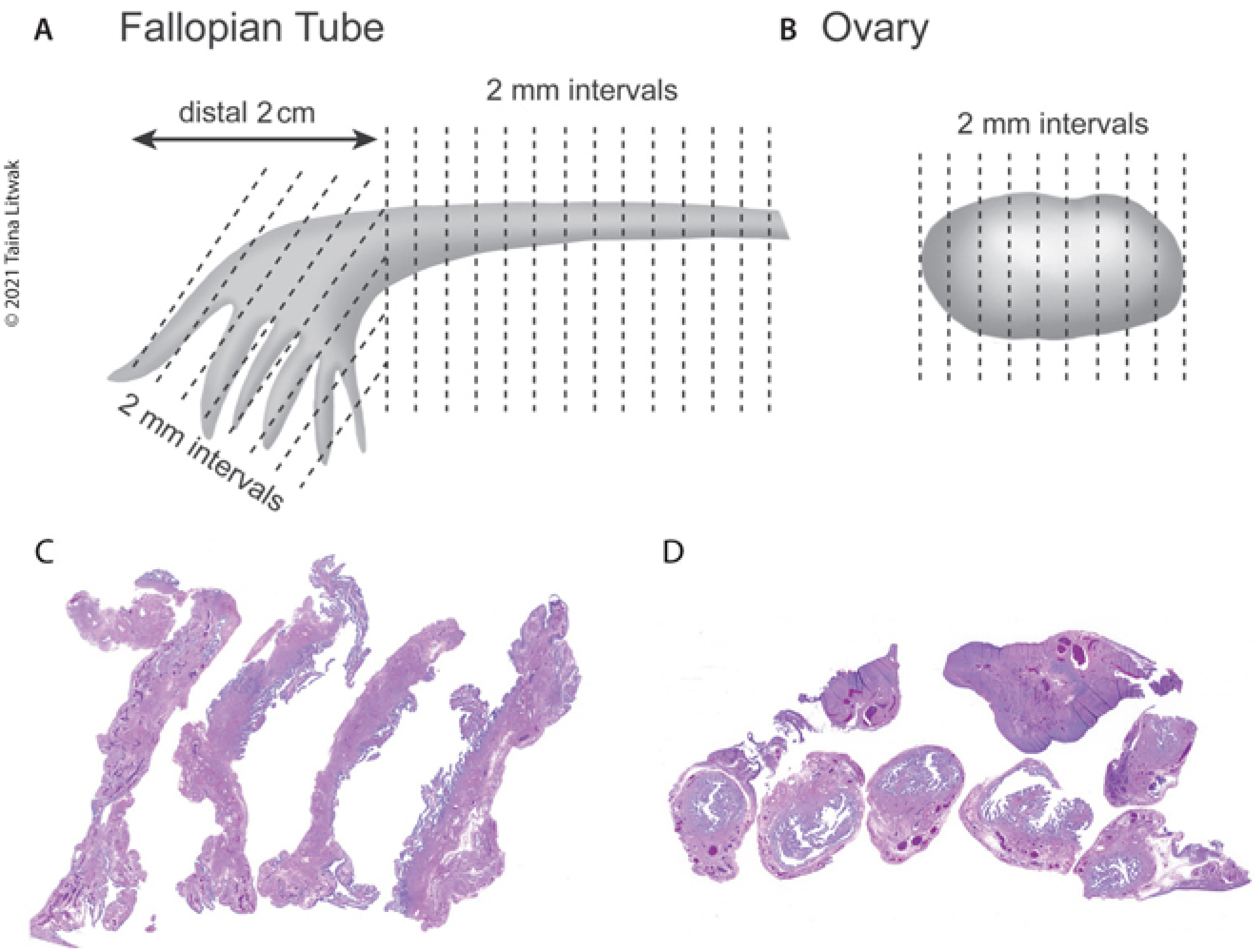

Figure 29-7. SEE-FIM protocol for grossing of risk-reducing salpingo-oophorectomy (RRSO) specimens. A: Serial sectioning of the fallopian tube at 2-mm intervals. The distal (fimbriated) end should be sectioned parallel to the long axis of tubal fimbria. The remaining mid and proximal portions are to be sectioned perpendicular to the lumen. B: The ovary should be sectioned at 2 mm intervals. C and D: Macroscopic images of glass slides showing the serially sectioned and entirely submitted fallopian tube from an RRSO specimen. C, fimbriated end; D, mid and proximal portion.

Sample gross description

Received fresh, labeled with the patient's name, medical record number and "right ovary and fallopian tube" is a 3.5 x 1.5 x 1 cm ovary with the attached fallopian tube, measuring 6.5 cm in length and 0.5 cm in diameter. The ovarian and tubal serosa are smooth and glistening, without any surface adhesions or irregularities. The specimen is fixed in formalin before sectioning. The ovary and fallopian tube are sectioned at 2-mm intervals according to the SEE-FIM protocol to reveal grossly unremarkable cut surfaces. The specimen is entirely submitted in six cassettes as follows: cassettes #1-2: fimbriated end of fallopian tube; cassettes #3-#4: remainder of fallopian tube; cassettes #5-6: ovary.

III. Common pathologic findings

RRSO specimens may harbor occult STIC or invasive HGSC in the fallopian tube and/or in the ovary. Immunohistochemical stains for p53 and Ki-67 may be helpful in confirming the diagnosis of STIC (Figure 29-3). Diagnostic criteria for STIC include marked nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, prominent nucleoli, loss of polarity, and increased mitotic activity. P53 immunostaining pattern is abnormal—most often strongly and diffusely positive, less often complete absence of staining—and Ki-67 shows at least 15% proliferation index. STIC only, even without stromal invasion, has the capacity for exfoliation and

transperitoneal metastatic spread; therefore, it should be staged as stage I (IA if unilateral, IB if bilateral, and IC3 if the peritoneal washings are positive).

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30. Trophoblastic Tumors

Pei Hui, MD

I. Indications

This tumor staging gross protocol should be used for surgical hysterectomy procedure for malignant gestational trophoblastic tumors, including invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The specimens may derive from various formats of hysterectomy, including abdominal and vaginal approaches (open, laparoscopic, or robotic assisted) with or without adnexae. The protocol may be used for curettage specimens when appropriate.[1,2]

II. What to expect to see macroscopically and microscopically

Single or multiple discrete masses or exophytic endometrial growth are typical presentation (Figure 30-1). Rare cases may have an endophytic/infiltrative growth pattern. Necrosis and hemorrhage may be extensive in the case of gestational choriocarcinoma. Neoplastic proliferations of various types of trophoblast are characteristically seen in trophoblastic tumors: sheets of triphasic proliferation of villous intermediate trophoblast, cytotrophoblast, and syncytial trophoblast in choriocarcinoma; nodular solid proliferation of implantation site intermediate trophoblast in placental site trophoblastic tumor; and nodular proliferation of chorionic-type intermediate trophoblast in epithelioid trophoblastic tumor .

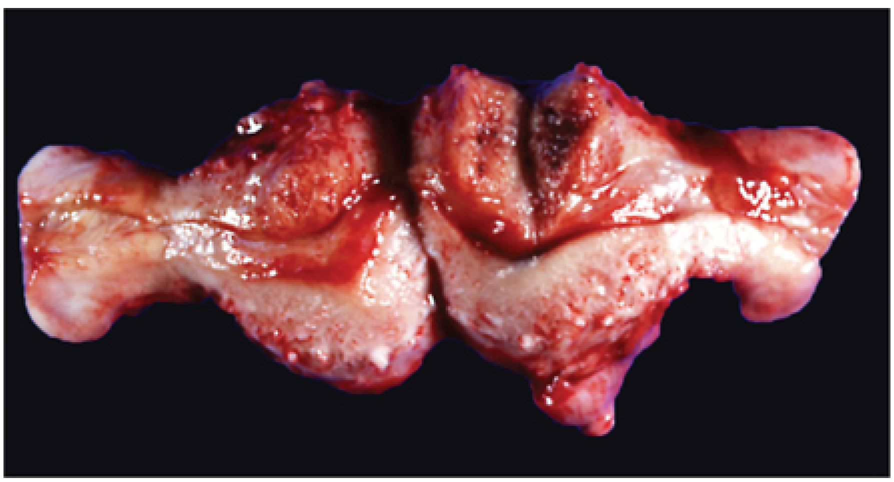

Figure 30-1. Placental site trophoblastic tumor (PSTT) presents as an intrauterine polypoid mass lesion with superficial myometrial invasion.

III. Dissection techniques: step-by-step description

1. Ideally, the uterus should be received intact and can be oriented to identify the anterior and posterior aspects. The presence of deeper peritoneal reflection indicates the posterior uterine surface. If the adnexa are attached, the ovary is located posterior to the fallopian tube. It is important to document if the uterus is received open or morcellated.

2. The entire specimen is weighed and the three dimensions of the uterus are measured to include the length, width between cornua, and anterior to posterior thickness in centimeters. Measure the diameter and the length of the cervix, and examine the cervical os for patency, noting its diameter.

3. Uterine serosal surface is inspected for color, texture, and presence of any adhesion, nodules, or cystic lesions. Note any gross lesions at the cervical os.

4. The uterus is opened coronally into anterior and posterior halves. To achieve this, a long thumb dressing forceps is inserted through the cervical canal to the fundus of the uterus, followed by sectioning using a sharp

blade to open the cervical canal and the endometrial cavity using the thumb dressing forceps as a guide (see Figure 28-2 in chapter 28).

5. The length of the cervical canal is measured, and cervical mucosa and stroma are inspected for lesions. The shape and size of the endometrial cavity are documented. Describe the location (fundus, entire cavity, or lower uterine segment) and the size of the gross lesion, if any, and presence or absence of gross tumor extension to the lower uterine segment and/or endocervix. The background endometrium is described with regard to color and thickness, texture of the endometrium is noted, and the presence of mucosal lesions and any distortion of the endometrial cavity by intramural or submucosal lesions are noted.

6. Anterior and posterior endomyometrium are serial sectioned. The cut surface of myometrium is inspected for color and texture and maximum thickness and the presence of mass lesion. Estimate the depth of carcinoma invasion in percentage of the thickness of myometrium. Trabeculation and nodularity (adenomyosis) and discrete, tan-white, rubbery nodules with whorled appearance (leiomyomata) are noted. The location (subserosal, intramural, submucosal, transmural) and any variation in the cut surface (necrosis, calcification, and hemorrhage) should be noted.

The following tissue sections should be embedded: anterior (12 o'clock) and posterior (6 o'clock) cervix, including transformation zone; submit at least four full-thickness sections to show the maximum depth of myometrial tumor invasion. Submit three or four additional sections of endometrium (not full thickness, multiple sections per cassette). If the uterine wall is too thick to fit in one cassette, a cross-section should be bisected and submitted in two adjacent cassettes and so noted in the gross description. Sections containing transitional areas (lesional to nonlesional areas) are helpful for measurement of myometrial invasion. Submit sections of any additional lesions, polyps, and leiomyomata. One section of anterior and one section of posterior lower uterine segment contiguous with upper endocervix are important for evaluation of cervical tumor extension. Separate standard anterior and posterior cervical sections are submitted. Representative sections of left and right parametrial soft tissue are also submitted, if present. Entire bilateral adnexae are submitted.

IV. Gross description using paragraph system

Received fresh, labeled with the patient's name and "uterus, ovaries and fallopian tubes" is total hysterectomy and bilateral salpingo-oophorectomy specimen, including uterus and its attached bilateral adnexae. The specimen weighs 50 grams. The corpus uterus measures 10.0 (cornua to cornua) x 6.5 (length) x 3.5 cm (anterior to posterior thickness). The uterine serosa is tan-pink and smooth. The whitish tan, glistening ectocervix (3.2 x 2.5 cm) displays an eccentric 0.6-cm slit-like os.

Sectioning reveals a 1.5 cm in length and 0.6 cm in diameter endocervical canal with tan-pink, slightly corrugated endocervical canal. The endometrial cavity (4.5 cm in length, 2.2 cm cornu to cornu) is distorted by a pink polypoid mass (4.2 x 4.0 cm) at the posterior endometrium. The mass is solid, pink on cut surface. The background endometrium is diffusely thickened with average thickness of 4 mm. The tan-red, trabeculated myometrium measures up to 3.5 cm thick.

Cut surface of myometrium demonstrates extension of the endometrial lesion to involve 50% of the anterior myometrium. The attached tan-yellow lobulated ovaries (1.5 x 1.0 x 0.4 cm on the right and 3.6 x 0.8 x 0.3 cm on the left) display a tan-yellow, smooth stroma upon sectioning and a 2.0-cm solid tan nodular lesion involving the left ovary. The attached tan-red fimbriated fallopian tubes (both measuring approximately 3.5 x 0.5 cm) display a stellate pinpoint lumen upon sectioning.

Representative sections are submitted in 22 cassettes as follows:

Cassette 1: Anterior cervix (12 o'clock)

Cassette 2: Posterior cervix (6 o'clock)

Cassette 3: Anterior lower uterine segment with extension to upper cervix

Cassette 4: Posterior lower uterine segment with extension to upper cervix

Cassettes 5-9: Anterior endomyometrial mass, including full thickness of myometrium to serosa

Cassettes 10-12: Remaining anterior endometrium

Cassettes 13-16: Posterior endomyometrium, including serosa

Cassettes 17-19: Sections of entire right ovary and fallopian tube
Cassettes 20-22: Sections of entire left ovary and fallopian tube

V. Common staging pitfalls and solutions

1. This protocol is not applicable to noninvasive hydatidiform moles. including complete and partial mole. Invasive mole is generally not a diagnosis made on curettage specimen.
2. Exaggerated placental site reaction and placental site nodule are benign conditions and therefore are not included in this protocol. However, the emerging concept of atypical placental site nodule may be considered as premalignant lesion.
3. Pathologic staging is determined by the tissue documentation of the anatomic extent of the tumor. However, histologic diagnosis of disease may not be available when abnormal human chorionic gonadotropin is observed clinically. If a biopsied tumor is not resected for any reason but the highest tumor T category is confirmed, pathologic staging should be performed without total removal of the primary lesion.
4. Lymphovascular invasion does not alter the T staging. In a setting of otherwise conventional molar gestations with or without myometrial invasion, the presence of lymphovascular invasion indicates an invasive mole.
5. Lymph node metastasis is not part of pT staging. Any lymph node metastasis is considered M1b disease
6. Involvement of genital organs is T2 tumor, but direct or metastasis to nongenital organs or tissues is classified as M1b, except lung metastasis as M1a.

VI. What to include in the pathology report

The final pathology report should include the following:

- Surgical procedures
- Hysterectomy type
- Specimen integrity
- Tumor size and location
- Histologic diagnosis
- Lymphovascular invasion
- Other peritoneal organs/tissue involvement, including ovaries, fallopian tubes, uterine serosa, omentum, and pelvic peritoneum.
- Surgical margins (cervical and parametrial surgical margins)
- Distant metastasis, including all nongenital organs and any lymph nodes
  - Lung metastasis
  - All other sites of metastasis
  - Number of metastases
- Other pathologic findings
- American Joint Committee on Cancer (AJCC) tumor staging/International Federation of Gynecology and Obstetrics (FIGO) staging

Samples of final diagnosis and synoptic report

Final diagnosis

Uterus, ovaries, and fallopian tubes; total hysterectomy and bilateral salpingo-oophorectomy

- Placental site trophoblastic tumor, 4.2 cm involving uterine corpus
- AJCC tumor staging (AJCC 8th ed): pT1M0; FIGO stage: I
- See synoptic report for details

Synoptic report

- Specimen: Uterus, ovaries, and fallopian tubes
- Procedures: Total hysterectomy and bilateral salpingo-oophorectomy
- Specimen integrity: Intact uterus
- Tumor site: Uterine corpus

- Tumor size: 4.2 cm
- Histologic type: Placental site trophoblastic tumor
- Myometrial involvement: Present
  - Depth of invasion: 2.5 cm
  - Myometrial thickness: 4.0 mm
- Uterine serosa: Not involved
- Lymphovascular invasion: Not identified
- Ovaries: Not involved by tumor
- Fallopian tubes: Not involved by tumor
- Distal cervical and parametrial soft tissue margins: Not involved
- Other findings: Left ovarian fibroma
- Pathologic stage (pTNM, AJCC 8th ed)
  - Primary tumor (pT): pT1
  - Distant metastasis: pM0
  - FIGO stage: I

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31. Uterine Cervix

Pei Hui, MD

I. Applications and indications[1-4]

This tumor staging protocol should be used for surgical staging hysterectomy procedure for invasive cervical carcinoma. The specimens may derive from various formats of radical hysterectomy (open, laparoscopic, or robotic assisted). Modified protocols are included for cervical conization and trachelectomy.

II. Gross specimen processing and documentation

Discrete cervical exophytic polypoid mass or endophytic/infiltrative growth with either no surface lesion or ulceration (Figure 31-1). Infiltrative mass lesion is often seen upon sectioning in advanced tumors.

Figure 31-1. Discrete cervical ulcerative lesion as example of cervical invasive adenocarcinoma. Note the underlying cervical stromal invasion.

Gross description

1. Ideally the uterus should be received intact and can be oriented to identify the anterior and posterior aspects. The presence of deeper peritoneal reflection indicates the posterior uterine surface. If the adnexae are attached, the ovary is located posterior to the fallopian tube. It is important to document if the uterus is received open or morcellated.

2. The entire specimen is weighed, and the three dimensions of the uterus are measured to include the length, width between cornua, and anterior to posterior thickness in centimeters. Measure the diameter and the length of the cervix and examine the cervical os for patency, noting its diameter and any lesion.

3. Uterine serosal surface is inspected for color, texture, and presence of any adhesion, nodules, or cystic lesions. The presence of parametrial tissue is noted and measured in three-dimensional volume.

4. The uterus is opened coronally into anterior and posterior halves. To achieve this, a long thumb dressing forceps is inserted through the cervical canal to the fundus of the uterus, followed by sectioning using a sharp blade to open the cervical canal and the endometrial cavity using the thumb dressing forceps as a guide (see Figure 28-2 in chapter 28).

5. The length of cervical canal is measured, and cervical mucosa and stroma are inspected for lesions. Describe the gross location and three dimensions of the tumor, including gross depth of tumor stromal invasion,

extension to lower uterine segment and endometrial cavity, and involvement of parametrium.

6. The shape and size of the endometrial cavity are documented. The background endometrium is described with regard to color and thickness, texture of the endometrium is noted, and the presence of mucosal lesions and any distortion of the endometrial cavity by intramural or submucosal lesions is noted.

Gross sectioning: step-by-step; sections submitted

Submit the entire cervical mucosa and vaginal cuff margin as a cone excision (see below) if the tumor is less than 4 cm in greatest dimension. Select representative sections if the tumor is greater than 4 cm. The representative sections should be submitted to demonstrate the depth of invasion and the relationship to the adjacent anatomic structures.

If the majority of the tumor is higher in the endocervical canal, additional sections should be taken in order to evaluate the depth of stromal invasion and extension to the lower uterine segment/endometrium.

Separate sections of left and right parametrial soft tissue (soft tissue adjacent to the cervix) are submitted, before submission of the cervical sections. Parametrial tissue must be inked.

Vaginal cuff margins, if present and wide enough (ie, wider than 10 mm), should be taken en face (usually four cassettes: V1-3, V4-6, V7-9, and V10-12); if thinner, vaginal cuff should be included with the cervical sections.

Modification for cervical conization specimens (Figure 31-2)

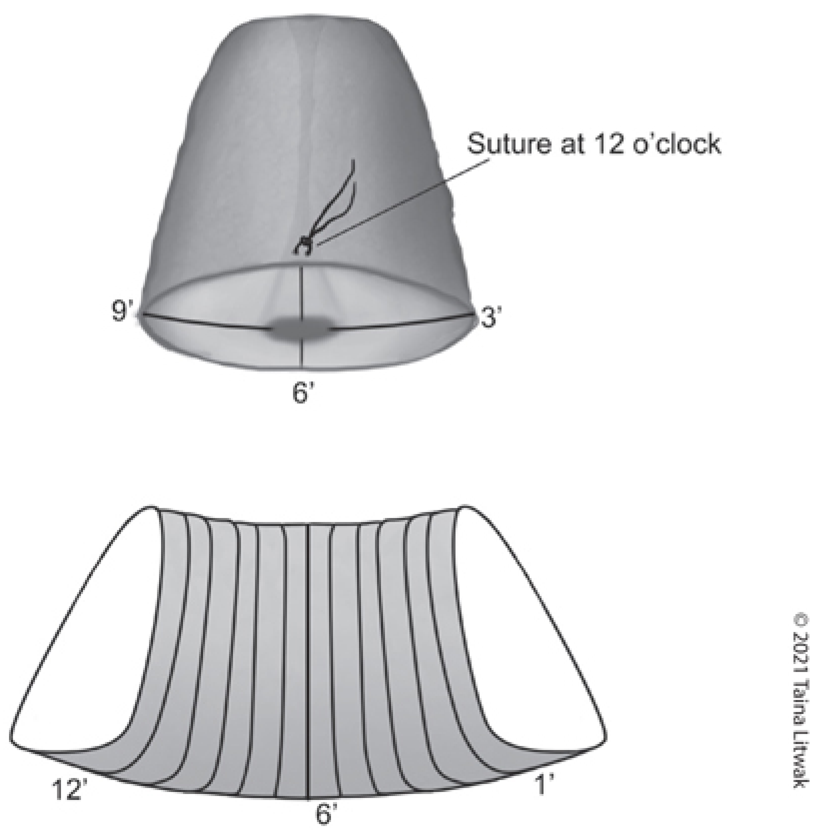

Figure 31-2. Gross processing of cervical cone excision. Frequently the specimen is oriented by suture at 12 o'clock position (top figure). The specimen is serially sectioned into 12 sections clockwise into 12 pieces (bottom figure).

Measure the diameters from 12 to 6 o'clock and from 3 to 9 o'clock, and the depth of the cone. Ink the surgical margins (endocervical aspect inked blue, ectocervical aspect inked black). Note any mucosal abnormalities. The specimen is usually oriented with a suture at 12 o'clock; open it at 12. If the specimen is not oriented, open it at an arbitrary point. Radially section and submit in 12 blue cassettes, with each cassette corresponding to the o'clock position.

Modification for cervical trachelectomy/radical trachelectomy specimen (Figure 31-3)

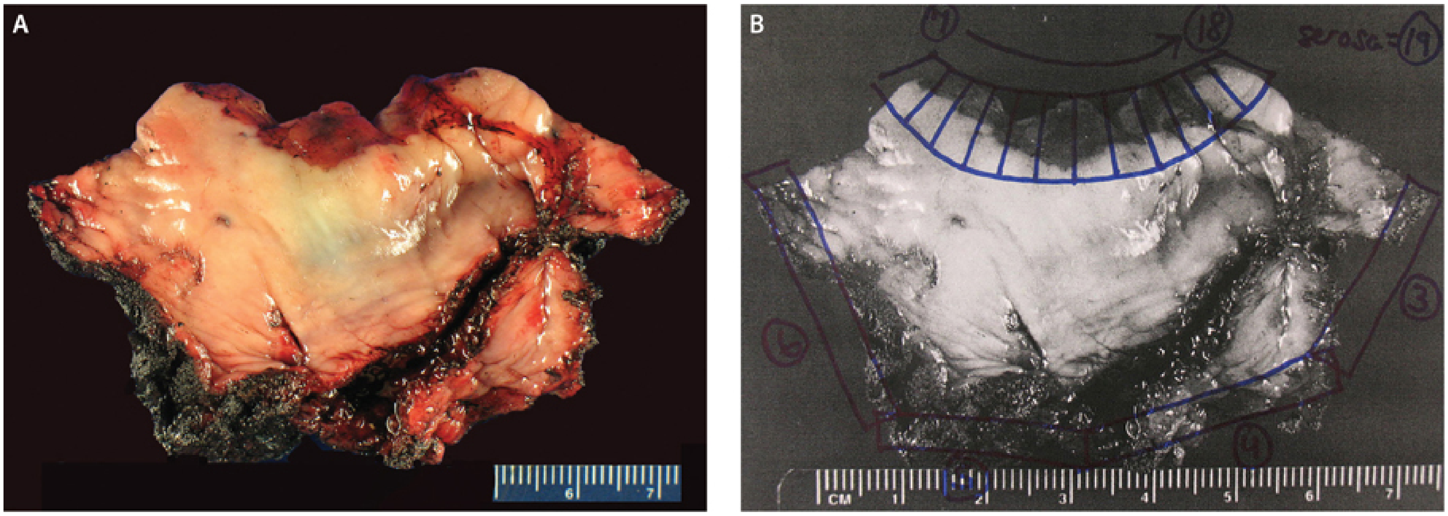

Figure 31-3. Gross processing of cervical trachelectomy specimen. Longitudinally opened cervix and associated distal lower uterine segment are presented (A). The cervical portion is submitted clockwise, similar to a cone specimen (B).

Measure the diameter and length of the cervix. Ink radial/parametrial soft tissue, distal ectocervical/vaginal cuff, and proximal endocervical margins. Obtain completely shaved endocervical margin and submit en face. Any mucosal abnormalities are noted. The specimen is usually oriented with a suture at 12 o'clock; open it at 12. If the specimen is not oriented, open it at an arbitrary point. Radial sectioning of the cervix includes distal ectocervical margin; submit in 12 cassettes, with each cassette corresponding to the o'clock position. Vaginal cuff margins, if present and wide enough (ie, wider than 10 mm), should be taken en face (usually four cassettes: V1-3, V4-6, V7-9, and V10-12); if thinner, vaginal cuff should be included with the cervical sections.

Sample gross description

Received fresh, labeled with the patient's name and "uterus, ovaries and fallopian tubes" is radical hysterectomy and bilateral salpingo-oophorectomy specimen, including uterus with attached bilateral adnexae. The specimen weighs 75 grams. The corpus uterus measures 8.0 cm (cornua to cornua) x 5.5 cm (length) x 4.5 cm (anterior to posterior thickness). The uterine serosa is tan-pink and smooth. The whitish-tan, glistening ectocervix (3.0 x 2.8 cm) displays an eccentric 0.5-cm slit-like os. The ectocervical mucosa and vaginal cuff appear smooth and unremarkable. The uterus is bivalved to reveal 0.9 x 0.7 cm indurated area at posterior transformation zone of cervix. Upon clockwise sectioning of the cervix, an underlying whitish firm lesion is seen with possible depth of invasion of 0.5 cm. The lesion grossly does not involve ectocervix and does extend to lower uterine segment. The endometrial cavity measures 4.5 cm in length, 2.2 cm cornu to cornu, with uniform granular endometrium of 0.2 cm in average thickness. The tan-red trabeculated myometrium measures up to 3.5 cm thick and shows no gross lesion upon sectioning. The attached parametrial tissue consists of fibrous soft tissue, measuring 3.2 x 2.2 x 1.0 cm (left) and 3.0 x 3.0 x 1.0 cm (right). The attached tan-yellow lobulated ovaries (1.5 x 1.0 x 0.4 cm on the right and 1.6 x 0.8 x 0.3 cm on the left) display a tan-yellow smooth stroma upon sectioning. The attached left fimbriated fallopian tube measures 6.0 cm in length and 0.6 cm in diameter and displays a 1.0-cm paratubal cyst and a stellate pinpoint lumen upon sectioning. The attached right fimbriated fallopian tube measures 5.0 cm in length and 0.5 cm in diameter, and displays a stellate pinpoint lumen upon sectioning.

Representative sections are submitted in 28 cassettes as follows:

Cassettes 1-6: Anterior cervix (12 to 5 o'clock)

Cassettes 7-12: Posterior cervix (6 to 11 o'clock) to include the entire lesion

Cassette 13: Anterior lower uterine segment with extension to upper cervix

Cassette 14: Posterior lower uterine segment with extension to upper cervix

Cassettes 15-16: Anterior endometrium, including serosa

Cassettes 17-18: Posterior endomyometrium, including serosa

Cassettes 19-20: Right parametrial tissue
Cassettes 21-22: Left parametrial tissue
Cassettes 23-25: Sections of entire right ovary and fallopian tube
Cassettes 26-28: Sections of entire left ovary and fallopian tube, including the paratubal cyst

Sample gross description for conization

Received in formalin, labeled with the patient's name and "LEEP," is a 3.0 x 2.5 x 1.5 (deep) cm tan conical tissue with a suture designating 12 o'clock. The surfacing mucosa is tan-pink, smooth, and glistening. The eccentric 0.5-cm slit-like os comes to within 0.4 cm of the 9 o'clock margin. The ectocervical margin is inked black, the endocervix is inked blue. The specimen is sectioned and entirely submitted in a clockwise fashion in 12 cassettes.

Sample gross description for radical trachelectomy

Received in formalin, labeled with the patient's name and "radical trachelectomy" is uterine cervix with attached parametrial soft tissue and thin rim of vaginal cuff. The cervix is 4.5 cm in length and 3.5 cm in diameter. A suture is seen designating 12 o'clock. The eccentric 0.5-cm slit-like os is present. Both distal vaginal cuff and proximal endocervical margins are inked black, and radial parametrial margin is inked blue. The proximal endocervical margin is shaved into two cassettes en face. The specimen is then coronally opened to reveal a 0.8-cm ulcerated mucosal lesion at 3 to 4 o'clock position, 2.5 cm from the distal vaginal cuff margin. The remaining cervical mucosa is tan-pink, smooth, and glistening. The parametrial soft tissue is striped into two cassettes. The cervical portion, including the ulcerated lesion and the distal vaginal cuff, is sectioned in a clockwise fashion into 12 cassettes (Figure 31-2). Representative sections of upper portion of the specimen are submitted.

III. Common potential staging pitfalls and solutions

1. Depth of tumor invasion (Figure 31-4)

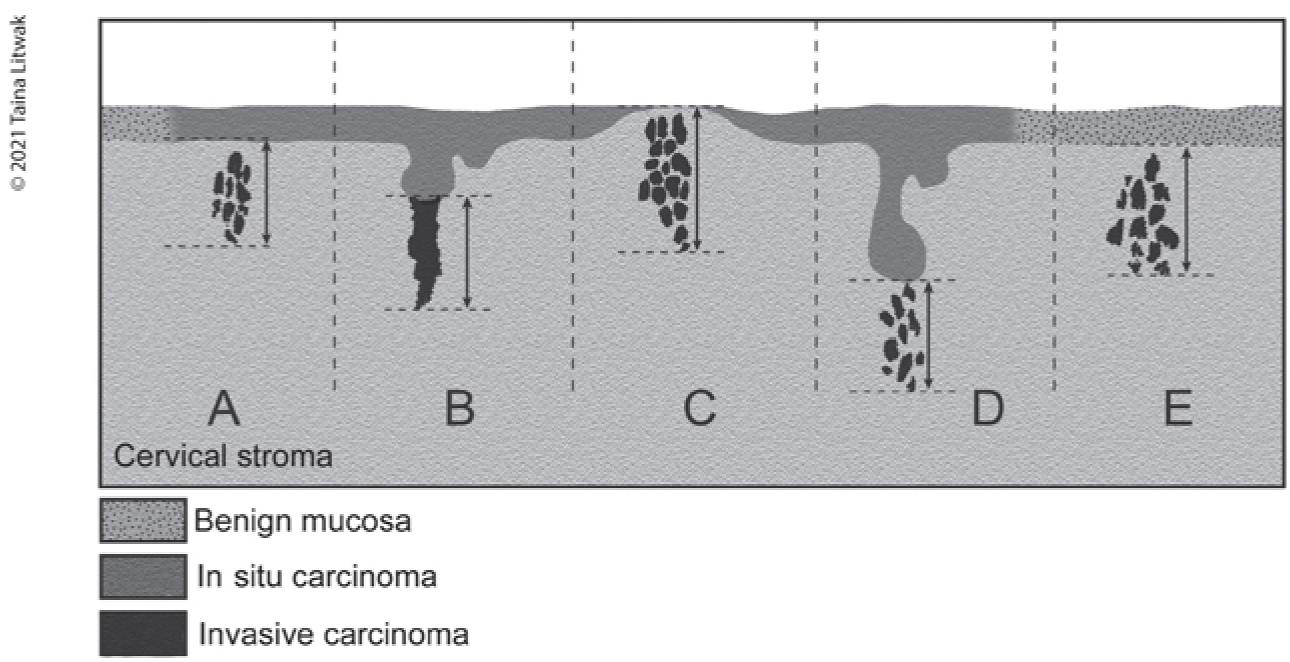

Figure 31-4. Diagram of microscopic measurement of extent of cervical carcinoma.

The depth of tumor invasion should be measured from the deepest invasive focus to the base of the intraepithelial lesion or, if no obvious in situ lesion, to the base of the nearest surface epithelium (Figures 31-4 and 31-5).

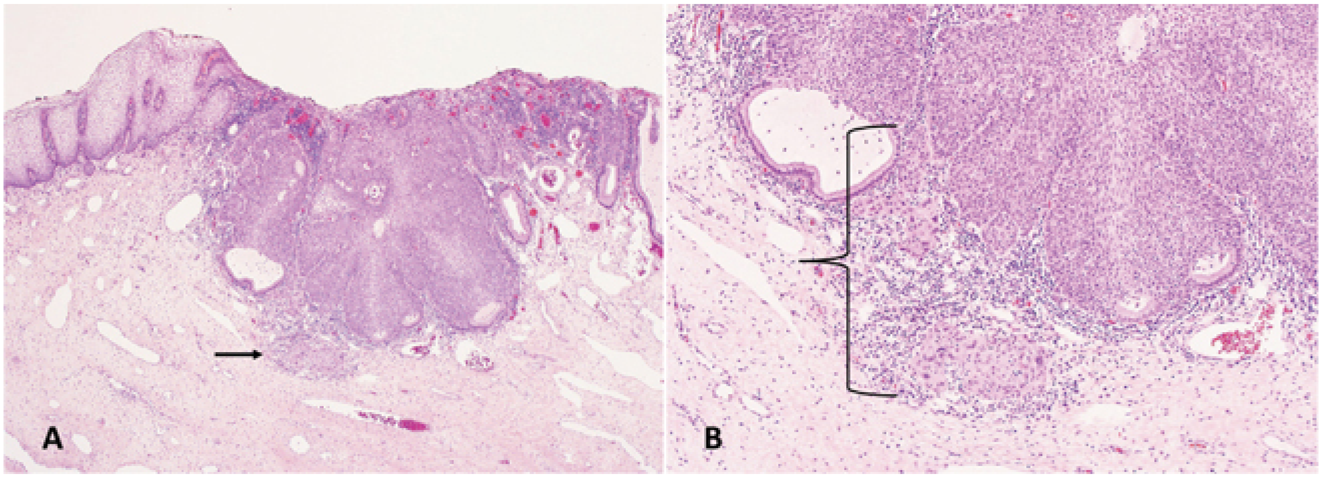

Figure 31-5. Measurement of depth of a superficial invasive squamous cell carcinoma (A, low power; B, high power).

In early invasive adenocarcinoma, the depth of invasion may be replaced by the thickness of lesion, in which invasive and in situ adenocarcinoma may be impossible to be separated from each other.

Likewise, depth of invasion may be replaced by tumor thickness when early invasive adenocarcinoma is recognized by its complex glandular architecture (extreme papillation or cribriforming) without infiltrative growth or stromal response.

2. Horizontal spread and third-dimension measurement

The width of invasion is measured to cover continued invasive glands without intervening in situ or normal areas (Figure 31-6).

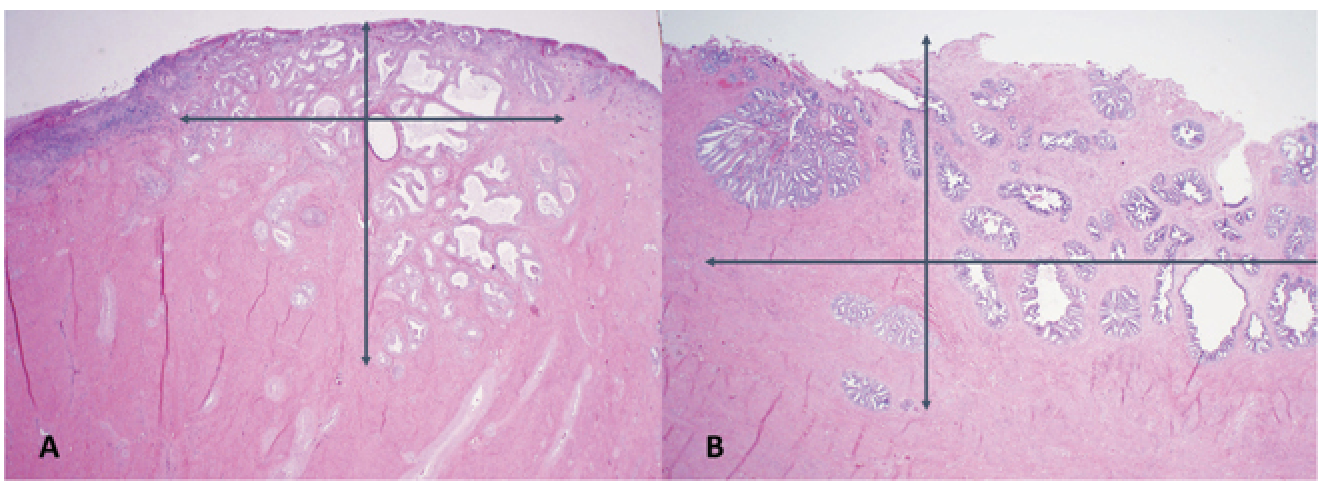

Figure 31-6. Measurement of depth and width of cervical invasive adenocarcinoma in these two examples (A and B).

In case of same invasive carcinoma focus involving consecutive sections of the cervix, adding the thickness of each section may surpass the greatest horizontal measurement on one section and therefore should be used to represent the maximal width of invasion.

3. Any clinically visible tumor or grossly visible lesion is stage IB tumor, regardless of the histologic measurement, even in the presence of superficial invasion (depth of <5 mm and/or width <7 mm).

4. Multifocal lesions

Multifocal invasion should be diagnosed with caution. It is recommended that foci are separated by at least 2-mm region/section without invasive lesion or foci are identified on separate lips of the cervix. Each focus must be reported separately.

Tumor staging of multifocal lesions is determined by measurement of the largest single focus or the focus that indicates the highest tumor stage.

5. Lymphovascular invasion

The number of foci of lymphovascular invasion (LVI) is clinically relevant in terms of likelihood of nodal metastasis.

6. Lymph node metastasis

Regional lymph node status must be included in the pathology report. Metastasis to lymph node(s) other than defined regional ones is considered M1.

7. Prior cervical excision

Histologic findings in a prior cone or loop biopsy may become essential to be included in the final hysterectomy staging in the determination of the overall tumor characteristics, tumor size, and stage.

8. Any gross visible lesions, even with superficial invasion, are stage IB tumor (Figure 31-1).

9. In case of biopsy-confirmed tumor that is not resected for any reason, if the highest stage tumor sites or lymph node involvement can be confirmed microscopically, pathologic staging should be reported even without the removal of the primary tumor.

IV. Essential components of the final pathology report

The final pathology report should include the following:

- Surgical procedures
- Hysterectomy type
- Specimens integrity
- Tumor size and location
- Depth of cervical stromal invasion
- Histologic diagnosis and grading
- Lower uterine segment involvement
- Uterine corpus extension (mucosa and myometrium)
- Parametrial involvement
- Surgical margins (distal cervical and parametrial margins)

If not involved, the closest distance to the margin in millimeters is documented.

- Lymphovascular invasion (LVI)

Although the presence of LVI does not change the tumor stage, the presence and number of foci of LVI should be reported.

- Other peritoneal organs/tissue involvement, including uterine serosa, ovaries, fallopian tubes, omentum, pelvic peritoneum, bladder, GI tracts, liver, pancreas, spleen, and so forth
- Pelvic lymph node status
  - Regional lymph nodes are strictly defined to include lymph nodes designated as pelvic, parametrial, obturator, internal, external iliac, common iliac, sacral, presacral, and para-aortic or periaortic lymph nodes.
  - Number of lymph nodes identified
  - Number of lymph nodes with metastatic tumor
  - Number of sentinel lymph node
  - Size of metastatic tumor in lymph node (isolated tumor cells: ≤0.2 mm or metastasis >0.2 mm)
- Distant metastasis (M1), including tumor involving organs/tissues beyond true pelvis, lymph nodes beyond the definition of regional lymph nodes (pelvic, parametrial, obturator internal iliac/hypogastric, external iliac, common iliac, sacral, presacral and para-aortic), and abdominal organs/tissues
- Peritoneal fluid/ascites cytology
- American Joint Committee on Cancer (AJCC) tumor staging/International Federation of Gynecology and Obstetrics (FIGO) staging

Samples of final diagnosis and synoptic report

Final diagnosis

Uterus, ovaries, fallopian tubes, omentum. and pelvic lymph nodes; radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node dissections

- Endocervical adenocarcinoma, usual histologic type and moderately differentiated
- Depth of invasion of 6.5 mm
- Metastatic carcinoma to 1 of 20 pelvic lymph nodes (1/20)
- AJCC tumor staging (AJCC Version 9): pT1b1N1M0; FIGO stage IIIC
- See synoptic report for details.

Synoptic report

- Specimen: Uterus, ovaries, fallopian tubes, omentum, and pelvic lymph nodes
- Procedures: Radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node dissections
- Specimen integrity: Intact
- Tumor site: Posterior cervix
- Tumor size: 9.0 mm
- Histologic type: Endocervical adenocarcinoma, usual type
- Histologic grade: Moderately differentiated
- Cervical stromal invasion: Present
  - Depth of invasion: 6.5 mm
- Parametrial involvement: Not identified
- Surgical margins: No ectocervical or radial margin involvement by either invasive or in situ adenocarcinoma
- Uterine serosa: Not involved by tumor
- Lower uterine segment involvement: Present
- Peritoneal/ascitic fluid: Negative for carcinoma
- Lymphovascular invasion: Present at four microscopic foci
- Ovaries: Not involved by tumor
- Fallopian tubes: Not involved by tumor
- Omentum: Not involved by tumor
- Regional lymph nodes:
  - Total number of lymph nodes examined: 20
  - Total number of lymph nodes involved: 1
  - Total left pelvic lymph nodes: 9
  - The number of pelvic lymph nodes involved: 1
  - Total right pelvic lymph nodes: 11
  - The number of pelvic lymph nodes involved: 0
- Other findings: Cervical adenocarcinoma in situ, uterine adenomyosis, and leiomyomas
- Pathologic stage (pTNM, AJCC Version 9)
  - Primary tumor (pT): pT1b1
  - Regional lymph nodes (pN): pN1
  - Distant metastasis: pM0
  - FIGO stage: IIIC1

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32. Uterine Sarcoma

Pei Hui, MD

I. Applications/indications[1,2]

This tumor staging gross protocol should be used for surgical staging hysterectomy procedures for various primary uterine sarcomas, including adenosarcoma (excluding c arcinosarcoma). The specimens may be derived from various types of hysterectomy, including abdominal and vaginal approaches (open, laparoscopic, or robotic assisted). This protocol does not apply to carcinosarcoma/malignant mixed Müllerian tumor (see hysterectomy protocol for endometrial carcinoma in chapter 28) or lymphomas.

II. Gross specimen processing and documentation

Various uterine mesenchymal malignancies may present destructive bulky masses involving endomyometrium, commonly leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma. Generally, uterine leiomyosarcomas present as a solitary large mass that has a fleshy, soft, and bulging cut surface with varying colors and textures. Infiltrative tumor border may be grossly apparent. Necrosis and hemorrhage are common (Figure 32-1). Myxoid leiomyosarcoma presents as a soft, gelatinous mass lesion with infiltrative border. Endometrial stromal sarcomas commonly display infiltrative, soft, tan myometrial lesion. Polypoid protrusion into the endometrial cavity can occur. On sections, grossly obvious myometrial and lymphovascular invasion in the form of worm-like plugs (Figure 32-2) is seen, which may extend into extrauterine vessels. Adenosarcoma often presents as a polypoid endometrial mucosal mass, and most cases are limited to the uterus at presentation. Presence of extrauterine tumor indicates sarcomatous overgrowth of adenosarcoma.

Figure 32-1. Uterine leiomyosarcoma presents as a solitary large mass that has a fleshy, bulging cut surface; necrosis and hemorrhage are common.

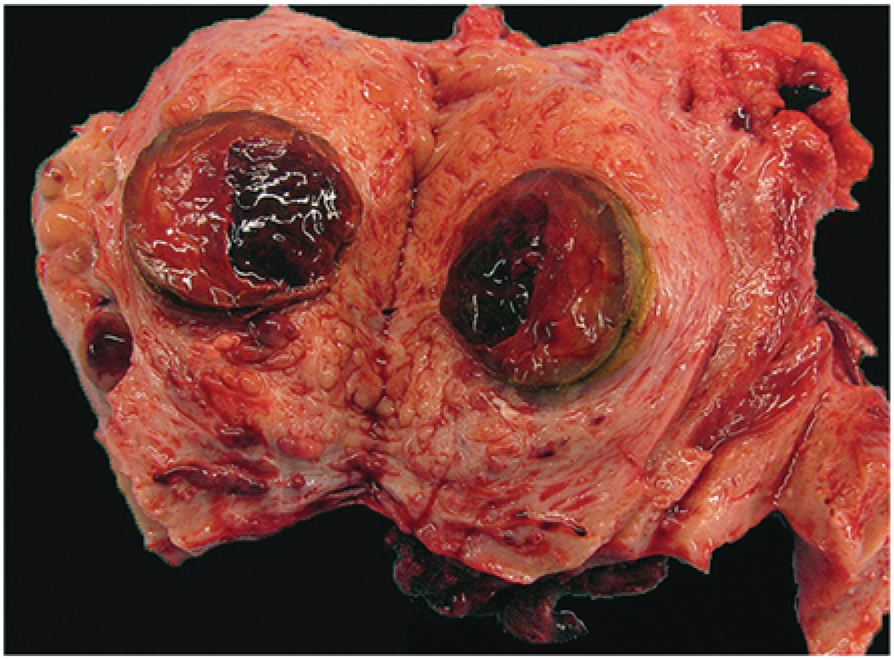

Figure 32-2. Low-grade endometrial stromal sarcoma is frequently an infiltrative myometrial lesion with gross myometrial and lymphovascular invasion in the form of worm-like plugs.

Gross description

1. Ideally, the uterus should be received intact and can be oriented to identify the anterior and posterior aspects. The presence of deeper peritoneal reflection indicates the posterior uterine surface. If the adnexae are attached, the ovary is located posterior to the fallopian tube. It is important to document if the uterus is received open or morcellated.

2. The entire specimen is weighed, and the three dimensions of the uterus are measured, to include the length, width between cornua, and anterior to posterior thickness in centimeters. Measure the diameter and the length of the cervix, and examine the cervical os for patency, noting its diameter.

3. Uterine serosal surface is inspected for color, texture, and presence of any adhesion, nodules, or cystic lesions. Note any gross lesions at the cervical os.

4. The uterus is opened coronally into anterior and posterior halves. To achieve this, a long thumb dressing forceps is inserted through the cervical canal to the fundus of the uterus, followed by sectioning using a sharp blade to open the cervical canal and the endometrial cavity using the thumb dressing forceps as a guide.

5. The length of the cervical canal is measured, and cervical mucosa and stroma are inspected for lesions. The shape and size of the endometrial cavity are documented. Describe the location (fundus, entire cavity, or lower uterine segment) and the size of the gross lesion, if any, and presence or absence of gross tumor extension to the lower uterine segment, endocervix, or uterine serosa. The background endometrium is described with regard to color and thickness, texture of the endometrium is noted, and the presence of mucosal lesions and any distortion of the endometrial cavity by intramural or submucosal lesions are noted.

6. Anterior and posterior endomyometrium are serial sectioned. The cut surface of myometrium is inspected for mass. The size of the tumor upon sectioning is measured to document the largest dimension. The location (subserosal, intramural, submucosal, transmural) and any variation in the cut surface (necrosis, calcification, and hemorrhage) should be noted. For adenosarcoma, the depth of myometrial invasion in percentage of the thickness of myometrium is noted.

Gross sectioning: step-by-step; sections submitted

The following tissue sections should be embedded: anterior (12 o'clock) and posterior (6 o'clock) cervix, including transformation zone; three or four sections of anterior and posterior endometrium, including underlying myometrium. If the uterine wall is too thick to fit in one cassette, a cross-section should be bisected and submitted in two adjacent cassettes and so noted in the gross description. Submit at least five full sections

of the myometrial mass lesion. Sections containing transitional areas (tumor and nontumor areas) are helpful for evaluation of tumor border. Submit sections of any additional lesions, polyps, and leiomyomata. One section of anterior and one section of posterior lower uterine segment contiguous with upper endocervix should be submitted. Separate standard anterior and posterior cervical sections are submitted. The entire bilateral adnexae should be submitted.

Sample gross description

Received fresh, labeled with the patient's name and "uterus, ovaries and fallopian tubes" is total hysterectomy and bilateral salpingo-oophorectomy specimen, including uterus and its attached bilateral adnexae. The specimen weighs 155 grams. The corpus uterus measures 11.0 cm (cornua to cornua) x 8.0 cm (length) x 10.0 cm (anterior to posterior thickness). The uterine serosa is tan-pink and smooth. The whitish tan, glistening ectocervix (3.0 x 2.8 cm) displays an eccentric 0.5-cm slit-like os. Sectioning reveals a 2.0 cm in length and 0.5 cm in diameter endocervical canal with tan-pink, slightly corrugated, endocervical canal. The endometrial cavity (4.5 cm in length, 2.2 cm cornu to cornu) is distorted by an anterior myometrial mass lesion. The endometrium is yellowish and relatively uniform in thickness of 0.3 cm. The tan-red trabeculated myometrium measures up to 7 cm thick. A solid mass measuring 9.5 x 8.0 cm involves anterior myometrium with tan to pink, bulging, fleshy cut surface and an irregular tumor border. Areas of hemorrhage and necrosis are identified. Several smaller myometrial nodules are also present, ranging from 0.5 to 3.0 cm in size with rubbery, whitish-tan cut surface. The attached tan-yellow lobulated ovaries (2.5 x 2.0 x 0.6 cm on the right and 2.6 x 1.8 x 0.5 cm on the left) display a tan-yellow smooth stroma upon sectioning. The attached tan-red fimbriated fallopian tubes (both measuring approximately 3.5 cm in length and 0.5 cm in diameter) display a stellate pinpoint lumen upon sectioning.

Representative sections are submitted in 21 cassettes as follows:

Cassette 1: Anterior cervix (12 o'clock)
Cassette 2: Posterior cervix (6 o'clock)
Cassette 3: Anterior lower uterine segment with extension to upper cervix
Cassette 4: Posterior lower uterine segment with extension to upper cervix
Cassettes 5-6: Anterior endomyometrium with full thickness of myometrium to serosa
Cassettes 7-8: Posterior endomyometrium with full thickness of myometrium to serosa
Cassettes 9-13: Sections of the largest myometrial mass
Cassettes 14-15: Sections of smaller myometrial masses
Cassettes 16-18: Sections of entire right ovary and fallopian tube
Cassettes 19-21: Sections of entire left ovary and fallopian tube

III. Common staging pitfalls and solutions

1. Leiomyosarcoma

- Leiomyosarcoma presents usually as a single large uterine mass or a predominant mass among background benign leiomyomas. Leiomyosarcomas are de novo, and malignant transformation from a benign leiomyoma is exceedingly uncommon, if exists.
- Histologic grading of leiomyosarcoma is unreliable. Once diagnosed, all are considered high-grade malignancy.
- Size of the tumor is an important prognostic parameter to be reported.

2. Endometrial stromal sarcoma

- Tumor border evaluation is crucial in separating endometrial stromal sarcoma from benign endometrial stromal nodule. Submission of entire or sufficient tumor border sections should be examined. The presence of greater than or equal to 3 mm of border invasion, three or more foci of border invasion of any depth, and lymphovascular invasion attests to the presence of endometrial stromal sarcoma.
- High-grade endometrial stromal sarcoma is currently defined by strict morphologic and molecular genetic characteristics.

3. Adenosarcoma

- Early adenosarcomas are polypoid mucosal lesions. Myometrial invasion signified stage IB (<50% myoinvasion) or stage IC (≥50% myoinvasion). Myoinvasion is recorded as percentage of myoinvasion over the total thickness of the myometrium where the deepest myoinvasion is found. Extrauterine disease signified sarcomatous overgrowth and therefore worse prognosis. Percentage of myoinvasion is not applicable or measured for the staging of other uterine sarcomas.
- The grade of the sarcoma may be documented as low (nuclear grade equivalent to low-grade endometrial stromal sarcoma) or high grade.
- Sarcomatous overgrowth is defined by the presence of pure (either high or low grade) sarcoma without glandular component, representing at least 25% of the tumor.

4. Perivascular epithelioid cell tumor is considered a potentially malignant tumor and should be staged as such.

5. In case of biopsy-confirmed tumor that is not resected for any reason, if the highest stage tumor sites or lymph node involvement can be confirmed microscopically, pathologic staging should be reported even without the removal of the primary tumor.

6. Simultaneous uterine and ovarian/pelvic peritoneal tumors with associated endometriosis should be classified as synchronous tumors[2]

IV. Essential components of the final pathology report

The final pathology report should include the following:

- Surgical procedures
- Hysterectomy types
- Specimen integrity
- Tumor size and location
- Histologic diagnosis and grading
- Depth of myometrial invasion (adenosarcoma only)
- Lower uterine segment involvement
- Cervical involvement
- Uterine serosa involvement
- Surgical margin involvement (location and distance to the closest margin if uninvolved)
- Lymphovascular invasion
- Other peritoneal organs/tissue involvement, including ovaries, fallopian tubes, omentum, pelvic peritoneum, bladder, gastrointestinal tract, liver, pancreas, spleen, and so forth
  - Tumor involving pelvic organs (adnexa or other pelvic tissue)
  - Number of sites of abdominal involvement (one site or more than one site)
  - Bladder and/or rectum mucosal involvement
- Pelvic lymph node status
  - Regional lymph nodes are strictly defined to include lymph nodes designated as pelvic, parametrial, obturator, internal or external or common iliac, sacral, presacral, and para-aortic or periaortic lymph nodes
  - Number of lymph nodes identified
  - Number of lymph nodes with metastatic tumor
  - Size of metastatic tumor in lymph node (isolated tumor cells ≤0.2 mm or metastasis >0.2 mm)
- Distant metastasis, including organs or tissue excluding pelvic and abdominal tissues/organs
- Peritoneal fluid cytology
- American Joint Committee on Cancer (AJCC) tumor staging/International Federation of Gynecology and Obstetrics (FIGO) staging

Samples for final diagnosis and synoptic report

Final diagnosis

Uterus, ovaries, fallopian tubes, and pelvic lymph nodes; total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissections

- Uterine leiomyosarcoma, 9.5 cm in size
- AJCC tumor staging (AJCC 8th ed): pT1bN0M0; FIGO stage: IB
- See synoptic report for details

Synoptic report

- Specimen: Uterus, ovaries, fallopian tube, and pelvic lymph nodes
- Procedures: Total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissections
- Specimen integrity: Intact uterus
- Tumor site: Anterior myometrium
- Tumor size: 9.5 cm
- Histologic type: Leiomyosarcoma
- Uterine serosa: Not involved
- Lower uterine segment involvement: Not involved
- Cervical involvement: Not identified
- Peritoneal/ascetic fluid: Negative for tumor
- Lymphovascular invasion: Not identified
- Ovaries: Not involved by tumor
- Fallopian tubes: Not involved by tumor
- Distal cervical and parametrial soft tissue margins: Not involved
- Regional lymph nodes
  - Total number of lymph nodes examined: 22
  - Total number of lymph nodes involved: 0
  - Total pelvic lymph nodes: 20
  - Total number of pelvic lymph nodes involved: 0
  - Total para-aortic lymph nodes: 2
  - Total number of para-aortic lymph nodes involved: 0
- Other findings: Endometrial polyp and uterine leiomyomas
- Pathologic stage (pTNM, AJCC 8th ed)
  - Primary tumor (pT): pT1b
  - Regional lymph nodes (pN): pN0
  - Distant metastasis: pM0
  - FIGO stage: IB

References

1. Krishnamurti U, Movahedi-Lankarani S, Bell DA, et al. Protocol for the examination of specimens from patients with primary sarcoma of the uterus. College of American Pathologists. 2018. Available at www.cap.org/cancerprotocols.
2. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th Ed. New York: Springer; 2017:671-680.

33. Vagina

Natalia Buza, MD

The surgical procedure performed for vaginal carcinomas depends on the location and extent of disease. Tumors located in the upper vagina may be treated by radical hysterectomy and partial (upper) vaginectomy and can be grossed in a similar manner to that of a radical hysterectomy specimen performed for cervical cancer (see chapter 31). Small (≤2 cm) tumors located in the mid to lower vagina may be resected by vulvovaginectomy. Radical vaginectomy with pelvic exenteration may be performed for recurrent or advanced vaginal cancer involving the bladder or rectum, with rectovaginal or vesicovaginal fistula. Regional (pelvic or inguinal) lymph node dissection is rarely performed, and sentinel lymph node biopsy is not part of the routine clinical practice for vaginal carcinomas. The International Federation of Gynecology and Obstetrics (FIGO) staging does not take regional lymph node involvement into account[1]; however, pelvic or inguinal lymph node metastases are staged as N1 (stage III) according to the American Joint Committee on Cancer (AJCC) cancer staging manual (8th ed). As with primary vulvar carcinomas, metastatic foci measuring not more than 0.2 mm should be considered isolated tumor cells and coded as “N0(i+).” For details on gross description and sectioning of lymph node dissections, see chapter 34.

Description of staging and reporting in this chapter includes carcinomas only; it excludes sarcomas and other tumor types.

I. Indications for the index specimen

Excision/partial vaginectomy

Partial vaginectomy/wide local excision may be performed for high-grade squamous intraepithelial lesion (HSIL)/vaginal intraepithelial neoplasia 2-3 (VAIN 2-3)/carcinoma in situ or small (≤2 cm), early stage, invasive carcinoma.

Radical vaginectomy/pelvic exenteration

Pelvic exenteration may be performed for recurrent or advanced vaginal cancer involving the bladder or rectum, with rectovaginal or vesicovaginal fistula, and occasionally for other advanced/recurrent gynecologic malignancies (ie, vulvar, cervical, endometrial, or ovarian primaries). The discussion in this chapter is limited to vaginal carcinomas. Anterior exenteration typically involves removal of the urinary bladder and urethra in addition to the anterior vagina, whereas the entire vagina, bladder, urethra, and anorectum are resected during total exenteration.

II. What do we expect to see in the (index) specimen macroscopically and microscopically?

Excision/partial vaginectomy

The partial vaginectomy specimen received for pathology examination is typically an elliptical or irregularly shaped portion of mucosa with varying amount of attached soft tissue. Gross examination may show an obvious exophytic mass lesion on the mucosal surface or an ill-defined surface irregularity. Ulceration may be present. The lesion may be grossly ill defined or may only appear as a depressed area or scar indicating the prior biopsy site. Microscopic examination may show in situ or early stage invasive squamous cell carcinoma or, less commonly, adenocarcinoma (clear cell, endometrioid, mucinous, or mesonephric histologic subtypes) or neuroendocrine carcinoma. In addition, precursor lesions—such as high-grade squamous dysplasia/in situ carcinoma or vaginal adenosis—may also be seen.[2]

Radical vaginectomy/pelvic exenteration

Radical vaginectomy with pelvic exenteration is one of the most complex specimens in gynecologic pathology. In addition to the vagina, the specimen may also contain the uterus, fallopian tubes, ovaries, urinary bladder, urethra, and rectum. Anterior pelvic exenteration includes only the urinary bladder (sparing the rectum), posterior exenteration includes only the rectum (sparing the urinary bladder), and total pelvic

exenteration includes removal of both the bladder and rectum. Gross examination typically shows a large, destructive, tumor mass originating from the vagina and invading adjacent structures, namely, the uterus, perivaginal soft tissue, bladder, or rectum. Vesicovaginal or rectovaginal fistula may be present.[3] Microscopically, carcinoma is present on multiple sections involving vagina, perivaginal soft tissue, and possibly the uterus, bladder, and rectum. Precursor lesions are less commonly identified because of overgrowth by the extensive invasive tumor component.

III. Typical macroscopic appearance of the (index) specimen

Excision/partial vaginectomy

The partial vaginectomy specimen received for pathology examination is typically an elliptical or irregularly shaped portion of mucosa with varying amount of attached soft tissue and can be handled in a manner similar to a partial vulvectomy specimen (see chapter 34). The specimen may be oriented by the surgeon with a stitch or multiple stitches.

Partial vaginectomy may also be performed along with radical hysterectomy; in such cases, a portion of upper vagina is attached to a radical hysterectomy specimen. If the tumor is located in the mid to lower vagina, it may be resected by vulvovaginectomy (see chapter 34).

Radical vaginectomy/pelvic exenteration

Radical vaginectomy with pelvic exenteration is a complex specimen containing the vagina and various combinations of other pelvic organs: uterus, fallopian tubes, ovaries, urinary bladder, urethra, and rectum. Anterior pelvic exenteration includes only the urinary bladder (sparing the rectum), posterior exenteration includes only the rectum (sparing the urinary bladder), and total pelvic exenteration includes removal of both the bladder and rectum.

IV. Dissection techniques: step-by-step description

Excision/partial vaginectomy

The gross description of partial vaginectomy should start with a three-dimensional measurement of the specimen, with specification of the depth of excision. The surgeon's stitch, if present, should be stated along with the orientation (clock face or anatomic) provided by the surgeon. After orientation, describe the size, number, and appearance of lesion(s) and gross distance of lesion(s) to the closest resection margins. Take gross photographs before inking and sectioning. The resection margins need to be inked, as for a skin ellipse, in two colors if the specimen is oriented (eg, 12-3-6 o'clock, or lateral/medial, or left/right—depending on the surgeon's orientation—in blue and 6-9-12 o'clock in black) but only in one color for an unoriented specimen. Larger specimens may be pinned flat and subjected to overnight fixation (Figure 33-1). Similar to a partial vulvectomy, smaller partial vaginectomy specimens should be serially sectioned ("bread-loafed") perpendicular to the long axis (see also chapter 34). Describe the cut surface of sections containing the lesion and, if present, the gross measurement of maximum depth of invasion. Submit the entire specimen, ideally with one section per cassette for optimal tissue embedding and cutting. The orientation of the submitted sections in each cassette should be clearly identified. Drawing a diagram or printing out the gross photograph to be used as a diagram may be helpful to indicate the location of each section taken. For close margins, submit sections perpendicular to the margins. If all margins are grossly widely clear, they can be submitted en face per diagram to indicate orientation, then followed by sectioning and submitting the center of the specimen to include the lesion with the deep margin.

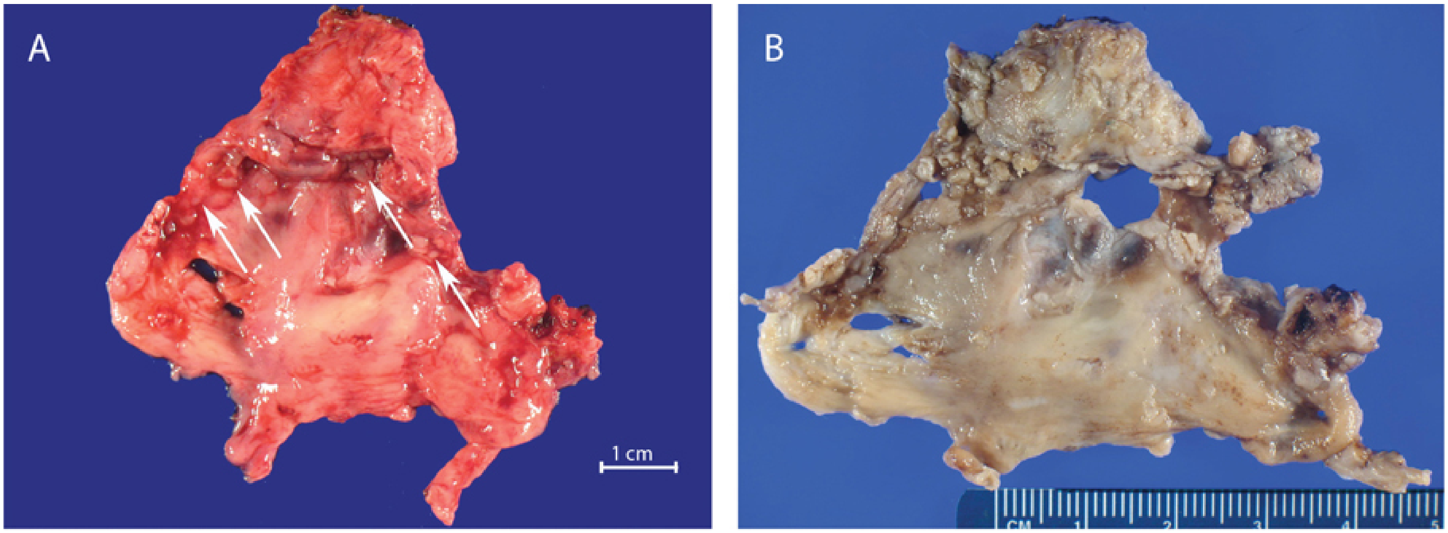

Figure 33-1. Partial vaginectomy for early-stage invasive squamous cell carcinoma before (A) and after formalin fixation (B). The mucosal surface shows several irregular, exophytic, hemorrhagic lesions (arrows) microscopically corresponding to foci of in situ and invasive carcinoma. The unoriented mucosal margins are positive for invasive carcinoma.

If the partial (upper) vaginectomy is received attached to a radical hysterectomy specimen, the uterus can be described similarly to a radical hysterectomy specimen performed for cervical cancer. Take gross photographs before inking and sectioning. The attached portion of upper vagina should be carefully measured, and the vaginal margins (mucosal and deep) should be inked. The uterus and attached vagina can be bivalved along the lateral aspects. Any gross lesions of the vaginal mucosa need to be described and measured. Distance of lesions to the nearest margins need to be documented. The specimen may be subjected to overnight formalin fixation to allow for easier sectioning (Figure 33-2A,B). If the vaginal mucosal margin is widely clear, submit the entire margin en face. For close margins, submit sections perpendicular to the margins. Take representative cervical sections contiguous with the vaginal mucosa to assess any cervical involvement and to rule out a potential cervical primary with vaginal extension. Take bilateral parametrial sections, including any potential lymph nodes. The remaining portion of the uterus can be sectioned and sampled as for benign uteri.

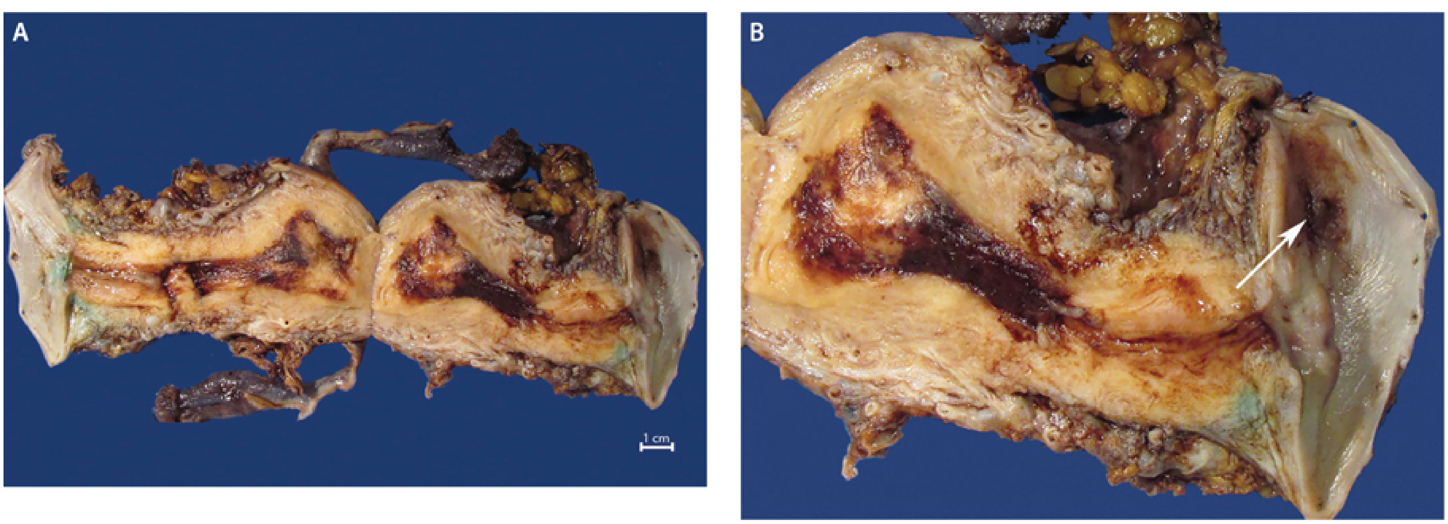

Figure 33-2. Partial (upper) vaginectomy with radical hysterectomy—photos taken after overnight formalin fixation (A, B). The specimen is bivalved to reveal a 1.5-cm, irregular, ulcerated lesion in the upper left vagina (B, arrow), microscopically corresponding to invasive squamous cell carcinoma. The ectocervical and endocervical mucosa are grossly uninvolved.

Radical vaginectomy/pelvic exenteration

The gross description of pelvic exenteration should start with an overall three-dimensional measurement and weight of specimen, followed by description and measurement of all grossly identifiable anatomical structures—for example, uterus, fallopian tubes, ovaries, vagina, bladder, urethra, and rectum. Take several gross photographs of the intact specimen before inking, sectioning and fixation. Describe any apparent tumor before sectioning.

Ink the resection margins: vaginal cuff, parametrial, intestinal, bladder/urethral, and soft tissue margins; multiple colors may be helpful to retain orientation after sectioning and fixation. Open the specimen: the vagina and uterus should be opened laterally, the bladder should be opened anteriorly with a Y incision, and the rectum should be opened posteriorly. Describe the tumor site, size, extent of involvement of various anatomical structures—particularly any obvious bladder or rectal mucosal involvement and/or ulceration—and relationship to resection margins. Use a probe to identify any vesicovaginal or rectovaginal fistulas. Describe any additional lesions. Take photographs of the opened specimen (Figure 33-3). Then the specimen should be pinned out and fixed in formalin overnight.

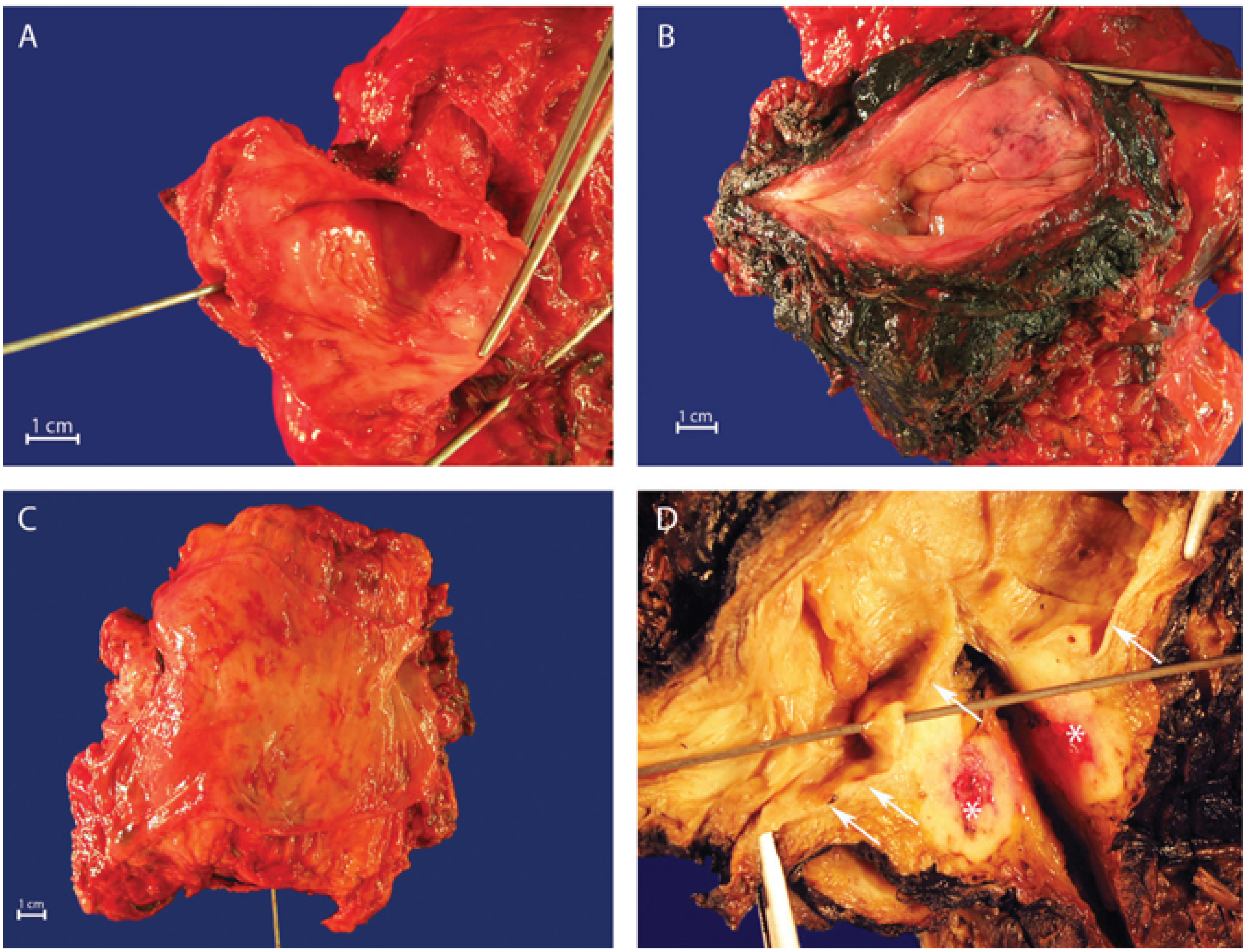

Figure 33-3. Total pelvic exenteration for advanced vaginal squamous cell carcinoma. Gross images before fixation show the vagina (A) partially opened, bladder (B) opened anteriorly, and rectum (C) opened posteriorly. Serial sectioning of the vagina after formalin fixation (D) reveals a firm tan-white tumor mass (*) extending from the vaginal mucosa (not shown) to the bladder wall (arrows). The overlying bladder mucosa is grossly intact. The probe is in one of the ureters.

After formalin fixation, start with submitting the margin sections first. If the vaginal mucosal margin is widely clear, submit the entire margin en face. For close margins, submit sections perpendicular to the margins. If the bowel margins are grossly widely clear, submit proximal and distal margins en face. Submit urethral and

bilateral ureteral margins en face. Submit representative, perpendicular, soft tissue margins closest to the tumor. After the margin sections have been submitted, carefully section through the tumor, evaluating the extent of involvement and determining the areas of tumor coming closest to the bladder and rectal mucosa. Submit sections from the tumor involving vagina, bladder, and rectum, focusing on areas closest to the bladder and rectal mucosal surface. Take representative cervical sections contiguous with the vaginal mucosa to assess any cervical involvement and to rule out a potential cervical primary with vaginal extension. Take bilateral parametrial sections, including any potential lymph nodes. The remaining portions of the uterus, bladder, and rectum can be sectioned and sampled as for benign specimens.

V. Gross descriptions using paragraph system

Excision/partial vaginectomy

Sample gross description

Received fresh, labeled with the patient's name, medical record number, and "uterus, bilateral fallopian tubes, cervix, and upper vagina" is a 160-gram radical hysterectomy and partial vaginectomy specimen consisting of the uterine corpus (6 x 5.5 x 3.5 cm), cervix (4 x 3 cm), attached upper vagina (ranging between 1.2 and 2.3 cm in length), and bilateral fimbriated fallopian tubes (averaging 6.5 x 0.8 cm). There is attached parametrial soft tissue bilaterally, averaging 2.5 x 2 x 1.8 cm. No parametrial lymph nodes are identified. The uterine serosa is smooth and glistening. The vaginal mucosal, deep, and parametrial margins are inked in black circumferentially, and the specimen is bivalved to show a 1.5- x 1-cm irregular, elevated, red-brown lesion on the posterior-left vaginal mucosa, coming to within 0.4 cm of the nearest left lateral vaginal mucosal margin. The ectocervical and endocervical mucosa are grossly unremarkable. The endometrial lining measures 0.3 cm in thickness. The myometrium is tan-pink, trabeculated, and measures 2.4 cm in thickness, without any gross lesions. Both fallopian tubes are serially sectioned and show pinpoint lumens without any gross abnormalities. Sectioning of the vaginal mucosa does not reveal any gross evidence of stromal invasion. Sections are submitted as follows: cassettes 1-2: anterior vaginal margin, en face; cassettes 3-4: posterior vaginal margin, en face; cassettes 5-9: vaginal mucosal lesion with deep margin; cassettes 10-13: representative sections of anterior and posterior cervix with adjacent vaginal mucosa; cassettes 14-17: left parametrium; cassettes 18-21: right parametrium; cassettes 22-25: representative sections of endomyometrium, including serosal surface; cassette 26: left fallopian tube; cassette 27: right fallopian tube.

Radical vaginectomy/pelvic exenteration

Sample gross description

Received fresh, labeled with the patient's name, medical record number, and "pelvic exenteration" is a 580-gram, 22 x 18 x 14 cm specimen consisting of a segment of rectum (13 x 6 x 4 cm), bladder (5 x 4 x 4 cm), urethral segment (1.7 x 1.2 x 1.2 cm), right ureter segment (2.8 x 0.6 cm), left ureter segment (3.2 x 0.6 cm), vagina (5 cm in length, 4.5 cm in diameter), and attached uterus (10 x 5.5 x 5 cm) with bilateral fallopian tubes (averaging 7 x 0.5 cm) and ovaries (averaging 2.5 x 1 cm). The vaginal margin is inked black, and the remaining soft tissue margins are inked blue. The urethra is probed, and the bladder is opened anteriorly to reveal a 0.8- x 0.5-cm ulcerated, irregular, firm red lesion on the posterior wall. The ureteral orifices are identified, and the ureters are probed bilaterally. The rectum is opened posteriorly to reveal a grossly unremarkable, tan-pink mucosa. The vagina and uterus are bivalved laterally, and a 5- x 3.5-cm firm, irregular, exophytic, tan-pink tumor is identified on the anterior vaginal wall, 0.7 cm from the nearest vaginal mucosal margin. The vaginal tumor is serially sectioned toward the bladder to reveal an ill-defined tan-white mass extending from the vagina to the ulcerated bladder mucosal surface. No definitive vesicovaginal fistula is identified. Cut sections of the posterior vaginal wall, rectum, uterus, ovaries, and fallopian tubes are without gross abnormalities.

Representative sections are submitted as follows: cassettes 1-2: anterior vaginal margin, en face; cassettes 3-4: posterior vaginal margin, en face; cassette 5: urethral margin, en face; cassette 6: left ureteral margin, en face; cassette 7: right ureteral margin, en face; cassette 8: proximal rectal margin, en face; cassette 9: distal rectal margin, en face; cassettes 10-12: closest perivaginal soft tissue margins; cassettes 13-16: vaginal tumor to

bladder; cassettes 17-18: ulcerated bladder lesion; cassettes 19-20: representative grossly uninvolved rectal mucosa; cassettes 21-23: representative sections of anterior and posterior cervix with adjacent vaginal mucosa; cassettes 24-27: representative sections of endomyometrium, including serosal surface; cassette 28: left fallopian tube and ovary; cassette 29: right fallopian tube and ovary.

VI. Common pathologic findings in the (index) specimen

Excision/partial vaginectomy

Based on the indication, common pathologic findings in partial vaginectomy specimens include HSIL/VAIN 2-3 and early stage invasive carcinoma. The most common type of primary vaginal malignancy is squamous cell carcinoma; adenocarcinomas—including clear cell, endometrioid, and mucinous, serous, and mesonephric subtypes—are much less common.

Radical vaginectomy/pelvic exenteration

The histologic findings in pelvic exenteration specimens depend on the clinical indication of the surgery. In addition to recurrent or advanced vaginal cancer, pelvic exenteration may also be performed for other advanced/recurrent gynecologic malignancies (eg, vulvar, cervical, endometrial, or ovarian primaries). The discussion in this chapter is limited to primary vaginal carcinomas. The most common type of primary vaginal malignancy is squamous cell carcinoma; vaginal adenocarcinomas, including clear cell, endometrioid, and mucinous, serous, and mesonephric subtypes, are much less common. Given the indication of the procedure, often there is extensive tumor infiltration involving the bladder and/or rectum and adjacent soft tissues.

VII. Common potential staging pitfalls and solutions

Excision/partial vaginectomy

Staging of early vaginal carcinomas is based on the tumor size (≤2 cm pT1a versus >2 cm pT1b), and, unlike cervical and vulvar carcinoma staging, it does not take depth of invasion into account. Thus, gross measurement and thorough correlation between gross and microscopic findings is crucial for accurate stage assignment. Involvement of paravaginal tissues, but not the pelvic sidewall, increases tumor stage to pT2 (≤2 cm pT2a and >2 cm pT2b). Pelvic sidewall involvement is considered pT3. Of note, pelvic sidewall is defined by the *AJCC Cancer Staging Manual* (8th ed) as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

Primary tumor site assignment is crucial for correct staging and optimal clinical management. Primary tumors of the vulva and cervix, especially squamous cell carcinoma, are much more common than vaginal primaries and may spread secondarily to the vagina, mimicking a primary vaginal malignancy. Absence of a cervical/vulvar primary and identification of a background vaginal in situ carcinoma helps confirm a vaginal primary (Figure 33-4). According to the FIGO system, tumors involving the vulva or cervix are not considered vaginal primaries and are classified as either primary vulvar or cervical malignancies.[4] In patients with history of prior gynecologic, lower gastrointestinal, or urologic malignancies, tumor recurrence or metastasis should be ruled out. Morphologic comparison with the patient's prior biopsy or resection material and immunohistochemical workup can be utilized in difficult cases[5] (Figure 33-5).

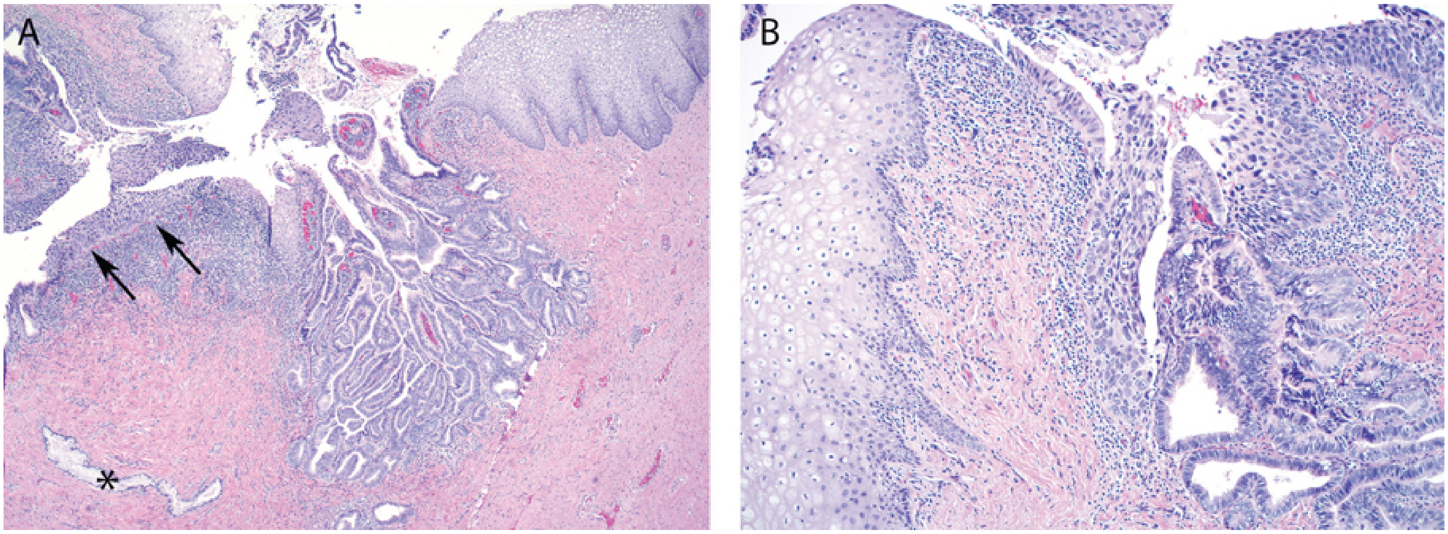

Figure 33-4. Partial vaginectomy showing endocervical-type adenocarcinoma. The patient had a history of total hysterectomy several years earlier. Microscopic images show background high-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia 3 (CIN3) in the vaginal mucosa (A, arrows) and background vaginal adenosis in the form of benign endocervical-type glands (A, *). Higher-magnification image (B) shows the abrupt transition from vaginal squamous mucosa (left) to in situ carcinoma (right).

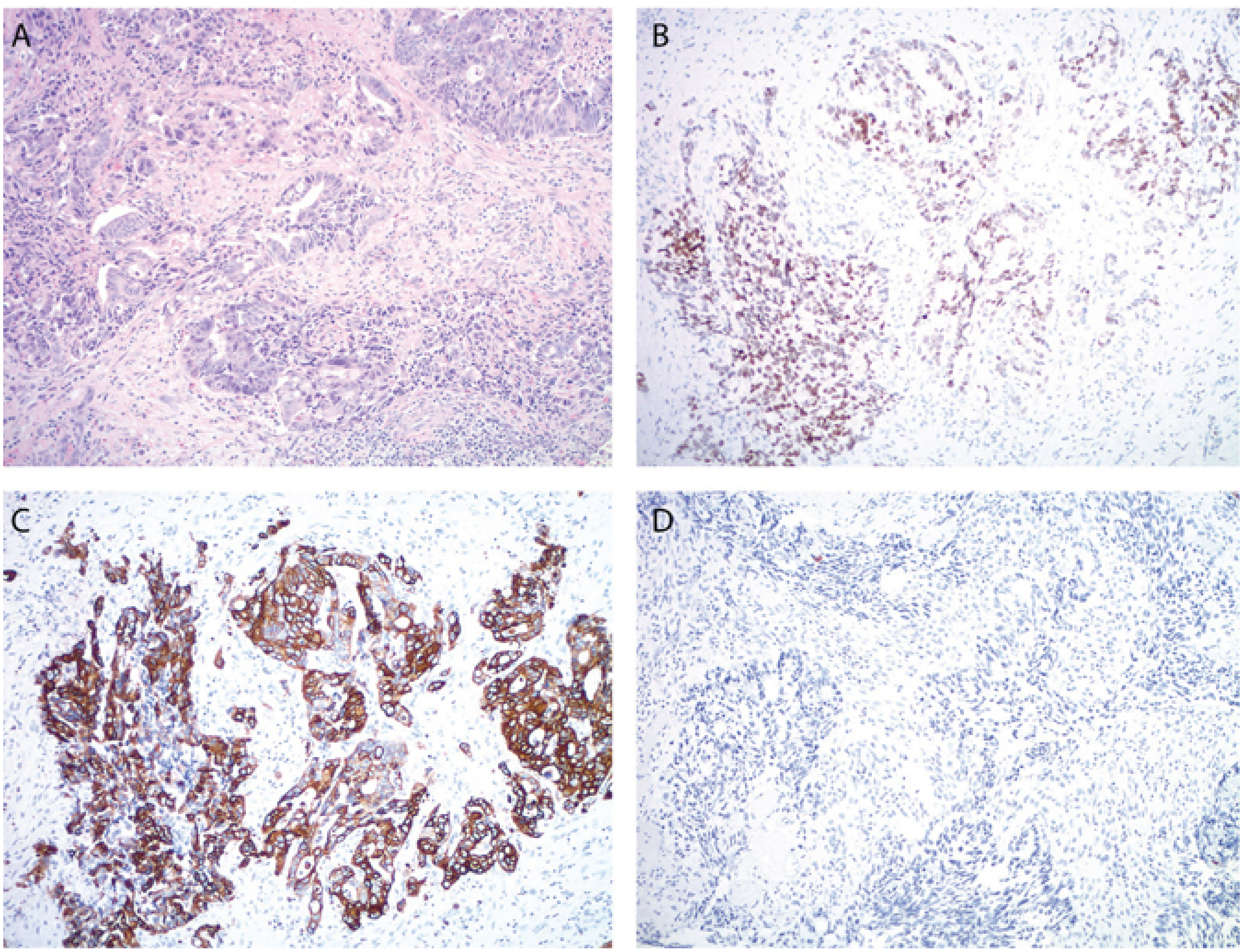

Figure 33-5. Vaginal mass excision in a patient with clinical history of rectal adenocarcinoma. The tumor is composed of markedly atypical cells forming irregular, infiltrative, glandular structures (A). The tumor cells are positive for CDX2 (B) and CK20 (C) immunostains and are negative for CK7 (D), confirming recurrence of the rectal primary and ruling out a primary vaginal adenocarcinoma.

Radical vaginectomy/pelvic exenteration

In addition to potential pitfalls encountered in partial vaginectomy specimens, documentation of bladder and/or rectal mucosal involvement is key to staging advanced vaginal carcinomas. Tumors with bladder or rectal mucosal involvement are staged as pT4.

VIII. What to include in the pathology report

Excision/partial vaginectomy

The final pathology report of a partial vaginectomy must include the following:

1. Sites/structures removed and procedure performed
2. Presence of in situ and/or invasive carcinoma
3. Histologic subtype and grade of invasive carcinoma
4. Maximum size of invasive carcinoma
5. Presence or absence of lymphovascular invasion
6. Presence or absence of paravaginal tissue involvement
7. Margin status (mucosal and deep margins)
   a. If negative, indicate the distance to the closest margin (optional)
   b. Indicate the location of the closest or positive margin

Samples for final diagnosis and synoptic report

Final diagnosis

Uterus, bilateral fallopian tubes, cervix, and upper vagina, radical hysterectomy and upper vaginectomy
- Invasive squamous cell carcinoma of the vagina
- Histologic type and grade: Keratinizing, moderately differentiated
- Tumor size: 1.5 cm
- Additional dimensions (optional): 1 cm x 0.3 cm (depth)
- Lymphovascular invasion: Not identified
- Paravaginal/parametrial involvement: Not identified
- Background HSIL (VAIN 3)
- All margins are negative for high-grade dysplasia and invasive carcinoma
- Additional findings
  - Inactive endometrium
  - Cervix, myometrium, uterine serosa, and bilateral fallopian tubes without significant abnormalities
- AJCC stage (8th ed): pT1a Nx, at least stage IA

Synoptic report

Specimen: Uterus, bilateral fallopian tubes, and upper vagina
Procedure: Radical hysterectomy and upper vaginectomy
Tumor site: Upper vagina, anterior wall
Tumor type: Invasive carcinoma
Histologic type: Squamous, keratinizing type
Histologic grade: Moderately differentiated
Tumor size: Greatest dimension: 1.5 cm; additional dimensions: 1 x 0.3 cm
Paravaginal/parametrial involvement: Not identified
Other tissue/organ involvement: Not identified
Margins: Negative
Lymphovascular invasion: Not identified
Associated epithelial lesions: HSIL (VAIN 3)
Pathologic staging (pTNM) primary tumor (pT): pT1a
Regional lymph nodes (pN): pNx
Number of lymph nodes examined: 0
Distant metastasis (pM): N/A

Radical vaginectomy/pelvic exenteration

The final pathology report of a pelvic exenteration for vaginal carcinoma has to include the following:

1. Sites/structures removed and procedure performed
2. Presence of invasive carcinoma
3. Histologic subtype and grade of invasive carcinoma
4. Maximum size of invasive carcinoma
5. Presence or absence of lymphovascular invasion
6. Presence or absence of paravaginal tissue involvement
7. Presence or absence of bladder and/or rectal involvement
   a. Extent of bladder and/or rectal involvement—specify if mucosal involvement is present
8. Presence of any precursor/in situ lesion
9. Margin status
   a. Vaginal
   b. Urethral
   c. Ureteral
   d. Rectal
   e. Soft tissue

Samples for final diagnosis and synoptic report

Final diagnosis

"Vagina, bladder, rectum, uterus, bilateral fallopian tubes and ovaries; pelvic exenteration
- Invasive squamous cell carcinoma of the vagina
- Histologic type and grade: Nonkeratinizing, poorly differentiated
- Tumor size: 6.5 cm
- Additional dimensions (optional): 3 cm x 3 cm
- Lymphovascular invasion: Identified
- Bladder involvement: Present, including bladder mucosa with surface ulceration
- Rectal involvement: Not identified
- Background HSIL (VAIN 3)
- All margins (including mucosal and soft tissue margins) are negative for invasive carcinoma
- Additional findings
  - Inactive endometrium
  - Cervix, myometrium, uterine serosa, and bilateral fallopian tubes and ovaries without significant abnormalities
- AJCC stage (8th ed): pT4 Nx, at least stage IVA"

Synoptic report

Specimen: Vagina, bladder, rectum, uterus, bilateral fallopian tubes and ovaries
Procedure: Pelvic exenteration
Tumor site: Upper vagina, anterior wall
Tumor type: Invasive carcinoma
Histologic type: Squamous, nonkeratinizing type
Histologic grade: Poorly differentiated
Tumor size: Greatest dimension: 6.5 cm; additional dimensions: 3 x 3 cm
Bladder involvement: Present, including bladder mucosa with surface ulceration
Rectal involvement: Not identified
Lymphovascular invasion: Identified
Margins: Negative
Associated epithelial lesions: HSIL (VAIN 3)
Pathologic staging (pTNM) primary tumor (pT): pT4
Regional lymph nodes (pN): pNx

Number of lymph nodes examined: 0
Distant metastasis (pM): N/A

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34. Vulva

Natalia Buza, MD

The surgical procedure performed for vulvar carcinomas depends on the location and extent of disease. In situ or early invasive carcinomas are typically removed by local excision or partial or total simple vulvectomy, whereas more advanced invasive carcinoma is treated with radical vulvectomy and regional lymph node sampling (sentinel lymph node or node dissection). The sections in this chapter are divided to provide detailed information about the four most common specimen types encountered at grossing: local excision/partial vulvectomy, simple/total vulvectomy, radical vulvectomy, and sentinel lymph node biopsy/node dissection.

Pathologic staging of primary vulvar carcinomas incorporates the tumor size (greatest horizontal extent); depth of invasion; for extensive tumors requiring radical vulvectomy, extension to adjacent perineal structures (vagina, urethra, and anus), rectum, bladder, or pelvic bone; and the lymph node status. Description of staging and reporting in this chapter excludes vulvar melanoma and sarcomas.

I. Indications for the index specimen

Local excision, wide excision, and partial vulvectomy

Local/wide excision or partial vulvectomy is typically performed for in situ or early stage invasive vulvar carcinoma and Paget disease with the intent to completely remove the tumor with negative margins.

Simple/total vulvectomy

Simple/total vulvectomy—complete removal of the entire vulva with some (superficial) subcutaneous tissue—is typically performed for extensive or multifocal involvement by preneoplastic lesions, in situ carcinoma, Paget disease, or early-stage invasive carcinoma. The urethra and vagina are spared. The clitoris may be spared, depending on the extent of disease and the patient's age.

Radical vulvectomy/anterior, posterior, or total

Radical vulvectomy includes complete removal of vulva and soft tissues down to the level of the deep perineal fascia. The typical indication for radical vulvectomy is invasive carcinoma. Depending on the tumor location and size, parts of the vulva may be spared (anterior/posterior radical vulvectomy, radical hemivulvectomy).

Regional lymph nodes: sentinel lymph node biopsy and node dissection

The inguinofemoral lymph node status is one of the most important prognostic factors of vulvar squamous cell carcinoma. Unilateral or bilateral sentinel lymph node biopsy is typically performed in patients with early-stage (stage IB or II) invasive carcinoma and no palpable inguinofemoral lymph nodes. Complete inguinofemoral lymph node dissection is usually performed in patients with confirmed positive lymph nodes.

II. What do we expect to see in the (index) specimen macroscopically and microscopically?

Local excision, wide excision, and partial vulvectomy

The excision specimen received for pathology examination is typically an elliptical portion of skin or mucosa, often with attached surgical sutures for orientation purposes. The skin/mucosal surface may show a grossly obvious exophytic mass lesion (Figure 34-1) or a flat ulcerated area. The lesion may be grossly ill defined or may only appear as a depressed area or scar indicating the prior biopsy site. Microscopic examination may show in situ or early-stage invasive squamous cell carcinoma, Paget disease with or without invasion, or, in some cases, scar only without residual carcinoma. Additional relevant microscopic findings also include other precursor lesions (eg, differentiated vulvar intraepithelial neoplasia [dVIN]) and lichen sclerosus.

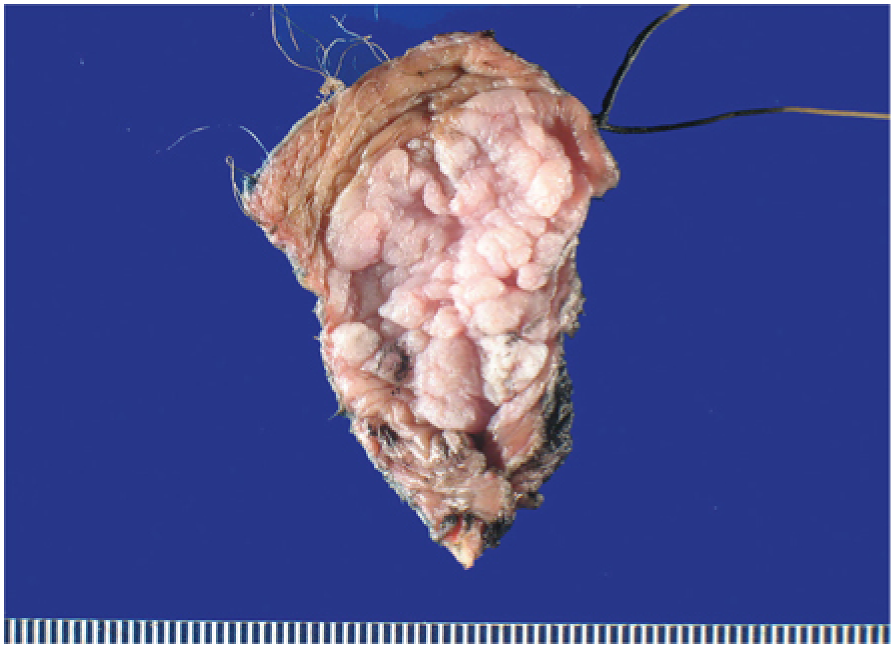

Figure 34-1. Right upper partial vulvectomy for vulvar intraepithelial neoplasia 3 (VIN 3). A stitch is present at the superior (periclitoral) aspect, as indicated by the submitting physician.

Simple/total vulvectomy

The specimen received for pathology examination typically consists of an ovoid portion of skin/mucosa with a central circular defect, corresponding to the incision around the urethral orifice and vagina. As with partial vulvectomy specimens, an obvious exophytic mass lesion or ulcerated flat area may be seen on gross examination. Paget disease grossly appears as an irregular, pink-red, ulcerated flat area on the skin and mucosal surfaces. Lesions may be multifocal, affecting the different anatomical sites of the vulva, often bilaterally. Background lichen sclerosus may be seen and grossly appears as an atrophic, shiny, hypopigmented area. As with partial vulvectomy, microscopic examination may show in situ or early stage invasive squamous cell carcinoma or Paget disease with or without invasion. Additional relevant microscopic findings also include other precursor lesions (eg, dVIN) and lichen sclerosus.

Radical vulvectomy/anterior, posterior, or total

Total radical vulvectomy typically consists of an ovoid portion of skin/mucosa with a central circular defect, corresponding to the incision around the urethral orifice and vagina with variable amount of subcutaneous and deep soft tissues attached (Figure 34-2). The specimen may also contain a portion of groin skin, the distal urethra, portion of vagina and/or anus, distal rectum, and en bloc inguinal and femoral lymph nodes. Gross exam typically reveals an obvious mass lesion, which is often exophytic and may show surface ulceration. Less commonly, carcinomas of the Bartholin gland may be surfaced by grossly unremarkable skin and can only be identified by palpation and serial sectioning. Microscopic examination demonstrates invasive carcinoma and, in most cases, associated precursor lesions (ie, basaloid/usual type VIN, dVIN, lichen sclerosus).

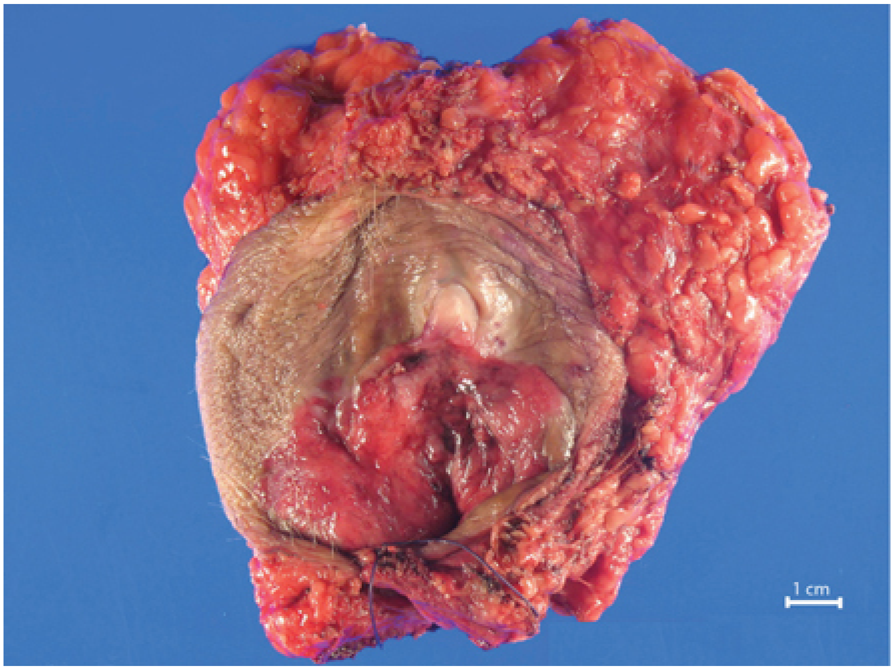

Figure 34-2. Radical total vulvectomy for invasive squamous cell carcinoma. Note the large ulcerated tumor involving bilateral labia minora, clitoris, and right labium majus. A large amount of subcutaneous and deep soft tissue is attached. A blue surgical stitch is placed posteriorly, indicating the perineal body inferior margin.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

Sentinel lymph node biopsy and lymph node dissection specimens consist of variably sized portions of fibroadipose tissue with embedded lymph nodes. Blue discoloration from the surgical dye (isosulfan blue or methylene blue) may be observed grossly in sentinel lymph nodes. On serial sectioning, firm tan-white areas may be grossly apparent, or several lymph nodes may be grossly matted, raising suspicion for involvement by metastatic carcinoma. Microscopic examination may reveal metastatic carcinoma, in some cases with extracapsular extension into the surrounding adipose tissue.

III. Typical macroscopic appearance of the (index) specimen

Local excision, wide excision, and partial vulvectomy

The excision specimen received for pathology examination is typically an elliptical portion of skin or mucosa and can be handled in a manner similar to that of a skin ellipse. Ideally, the specimen is oriented by the surgeon with a stitch or multiple stitches (Figure 34-1).

Simple/total vulvectomy

The specimen received for pathology examination typically consists of an ovoid portion of skin/mucosa with a central circular defect, corresponding to the incision around the urethral orifice and vagina (Figure 34-3A,B). The specimen may be oriented by the surgeon with a stitch or multiple stitches.

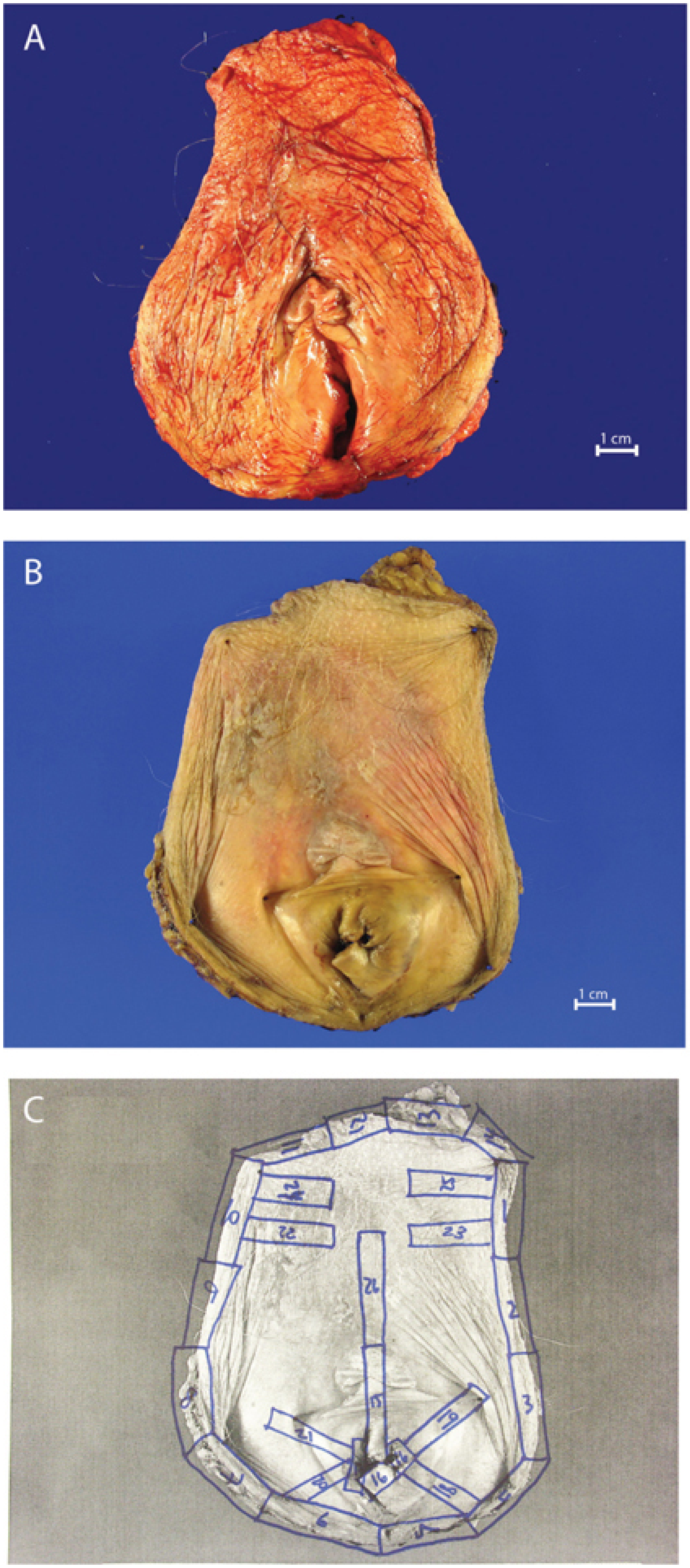
A
1 cm
B
1 cm
C

Figure 34-3. Simple vulvectomy for Paget disease, before (A) and after formalin fixation (B). The printed image of the specimen can be used as a diagram to indicate the location of each section taken (C).

Radical vulvectomy/anterior, posterior, or total

Total radical vulvectomy typically consists of an ovoid portion of skin/mucosa with a central circular defect, corresponding to the incision around the urethral orifice and vagina. There is a variable amount of subcutaneous and deep soft tissue attached (Figure 34-2). The specimen may be oriented by the surgeon with a stitch or multiple stitches. Depending on the site and extent of disease, a portion of groin skin, the distal urethra, portion of vagina and/or anus and distal rectum may also be resected. It is helpful to read the operative note or consult the surgical team before grossing complex resection specimens.

The radical vulvectomy specimen may also contain en bloc inguinal and femoral lymph nodes or the nodes may be sent separately for pathology evaluation.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

Sentinel lymph node biopsy and lymph node dissection specimens consist of variably sized portions of fibroadipose tissue with embedded lymph nodes. Blue discoloration from the surgical dye (isosulfan blue or methylene blue) may be observed grossly in sentinel lymph nodes.

IV. Dissection techniques: step-by-step description

Local excision, wide excision, and partial vulvectomy

The gross description of partial vulvectomy should start with a three-dimensional measurement of the specimen, with specification of the depth of excision. The surgeon's stitch, if present, should be stated along with the orientation (clock face or anatomical) provided by the surgeon. After the orientation, describe the size, number, and appearance of lesion(s) and gross distance to the closest resection margins. Take gross photographs before inking and sectioning.

The resection margins need to be inked, similar to a skin ellipse, in two colors if the specimen is oriented (eg, 12-3-6 o'clock or lateral/medial or left/right—depending on the surgeon's orientation—in blue and 6-9-12 o'clock in black) or in one color for an unoriented specimen. Larger specimens may be pinned flat and subjected to overnight fixation.

Smaller excision specimens should be serially sectioned ("bread-loafed") perpendicular to the long axis (Figure 34-4). Describe the cut surface of sections containing the lesion and, if present, the gross measurement of maximum depth of invasion. Submit the entire specimen, ideally with one section per cassette for optimal tissue embedding and cutting. The orientation of the submitted sections in each cassette should be clearly identified (see sample gross dictation). Drawing a diagram or printing out the gross photograph to be used as a diagram may be helpful to indicate the location of each section taken (Figure 34-5).

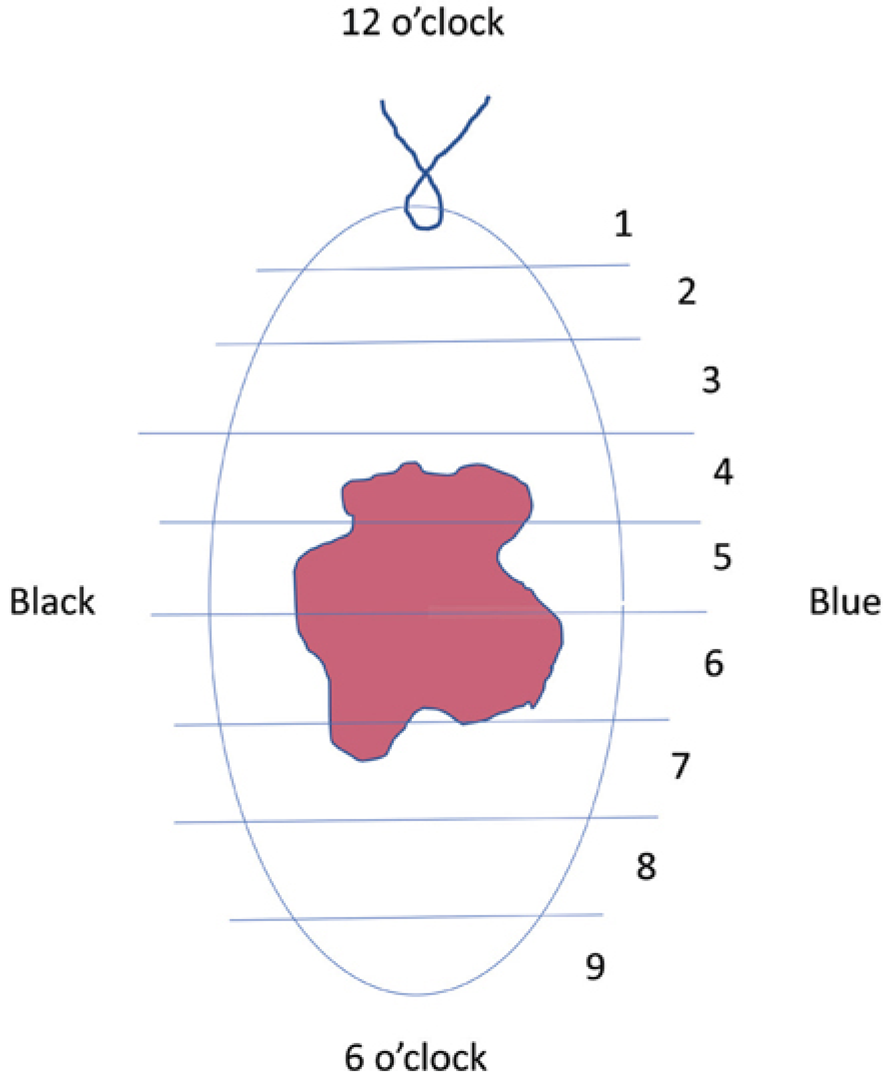

Figure 34-4. Diagram for grossing and sectioning of a small oriented partial vulvectomy specimen.

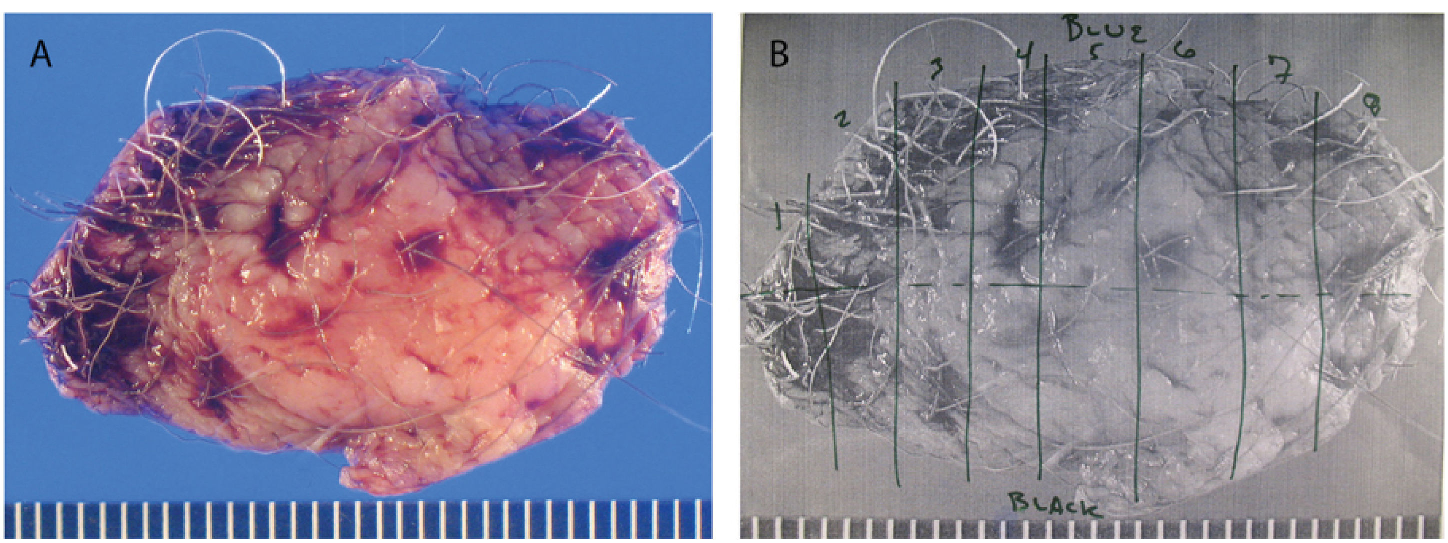

Figure 34-5. Right partial vulvectomy for early invasive squamous cell carcinoma. This specimen, before fixation, is showing an exophytic, focally ulcerated tumor (A). The specimen was serially sectioned and entirely submitted per diagram (B).

If the specimen is too large for serial sections to fit entirely into a cassette, then draw a diagram or print out the gross photograph to be used as a diagram to indicate the location of each section taken. For close margins,

submit sections perpendicular to the margins. If all margins are grossly widely clear, they can be submitted en face per diagram to indicate orientation, then followed by sectioning and submitting the center of the specimen to include the lesion with the deep margin (Figure 34-6).

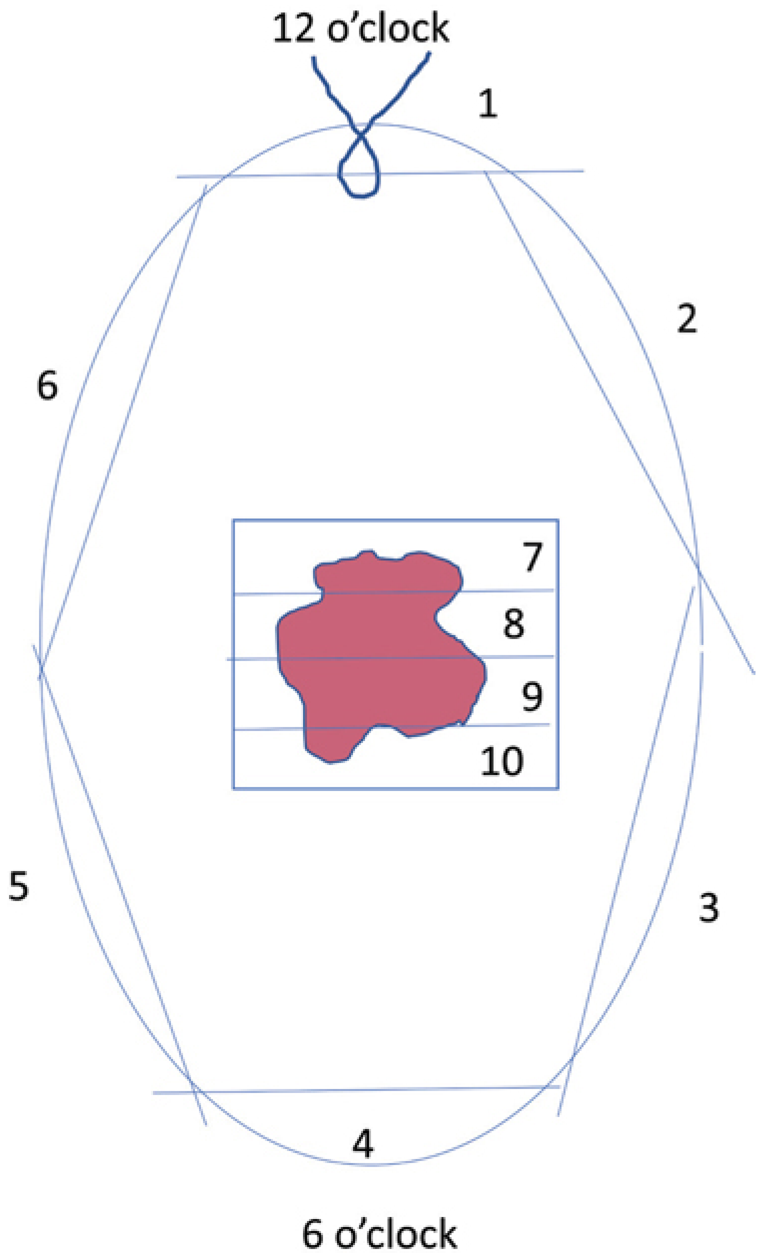

Figure 34-6. Diagram for grossing and sectioning of a larger, oriented partial vulvectomy specimen.

Simple/total vulvectomy

The gross description of total simple vulvectomy should start with a three-dimensional measurement of the specimen, with specification of the depth of excision. The surgeon's stitch, if present, should be stated along with the orientation provided by the surgeon. Contact the surgical team if there are any questions regarding specimen orientation. Describe the anatomical structures present (ie, clitoral hood, labia majora, labia minora) and the size, number, location, and appearance of lesion(s) and gross distance to the closest resection margins. Take gross photographs before inking and fixing the specimen (Figure 34-3A).

The resection margins need to be inked: one color can be used for inking the deep margin and circumferential skin margins and a second color for inking the vaginal resection margin. Total vulvectomy specimens should be pinned flat and subjected to overnight fixation before sectioning.

A diagram of the specimen—either a drawing or a copy of the gross photograph—should be used to indicate the location of each section taken (Figure 34-3B,C).

Start with sectioning and submitting the margin sections. For close margins, submit sections perpendicular to the margins to include the lesion and the inked margin. If all margins are grossly widely clear, they can be submitted en face per diagram to indicate their orientation. Margin sections should include circumferential skin margins and vaginal resection margins. For multifocal and/or grossly ill-defined lesions (eg, Paget disease), it is reasonable to submit the entire circumferential skin and vaginal margins. For well-defined lesions, selective margin sections for the closest margins are appropriate. Next, section the lesion(s), and evaluate the cut surfaces for the maximum gross depth of invasion. Submit sections from the lesion(s) to include the greatest depth of invasion, if present. Submit sections from any other suspicious areas. If no definitive lesions are identified, submit random sections from both labia majora and minora, clitoris, and anterior and posterior fourchettes.

Radical vulvectomy/anterior, posterior, or total

A diagram of the specimen—either a drawing or a copy of the gross photograph—should be used to indicate the location of each section taken (Figure 34-7A,B).

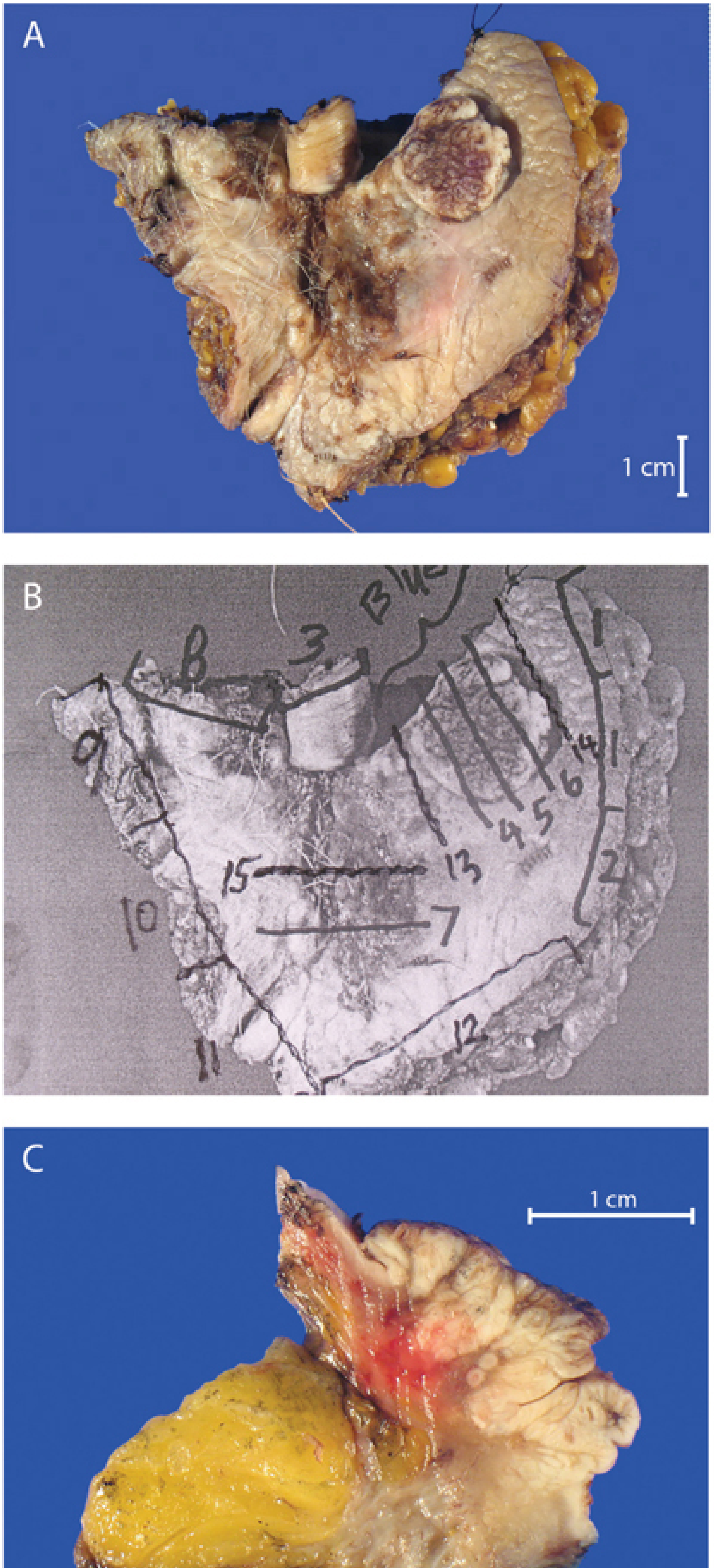
A
1 cm
B
C
1 cm

Figure 34-7. Radical posterior vulvectomy for multifocal invasive squamous cell carcinoma (A). The printed image of the specimen can be used as a diagram to indicate the location of each section taken (B). Close margin should be submitted as perpendicular sections (sections 4-6), whereas other margins can be submitted en face. Serial sectioning of the tumor shows a tan-white cut surface with approximately 0.7 cm depth of invasion grossly (C).

Start with sectioning and submitting the margin sections. For close margins, submit sections perpendicular to the margins, to include the lesion and the inked margin. If all margins are grossly widely clear, they can be submitted en face per diagram to indicate their orientation. Margin sections should include representative perpendicular or en face circumferential skin margins, entire vaginal resection margin (perpendicular or en face), and other—urethral, anal, or rectal—margins, perpendicular or en face, depending on the tumor proximity to the margin. The urethra can be probed to facilitate gross sectioning.

Next, section the lesion(s) and evaluate the cut surfaces for the maximum gross depth of invasion (Figure 34-7C). Submit sections from the lesion(s) to include the greatest depth of invasion, if present. Submit sections from any other suspicious areas. If no definitive lesions are identified, submit random sections from both labia majora and minora, clitoris, and anterior and posterior fourchettes. Submit additional sections from urethra, anus, and rectum to assess tumor extension to these structures. Tumors involving adjacent perineal structures (distal third of urethra and/or vagina, and/or anus) are staged as pT2, regardless of their size.

Carefully dissect the attached adipose tissue to identify any lymph nodes. For detailed handling of regional lymph nodes, see the next section.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

Start the gross description with the three-dimensional measurement of specimen. The individual lymph nodes need to be dissected carefully from the adipose tissue, leaving the capsule intact, ideally with a thin rim of attached fat to allow for evaluation of potential extracapsular extension. Describe the number and size range of dissected lymph nodes. Describe the cut surfaces of lymph nodes and comment on any firm, white foci grossly suspicious for metastatic disease. In sentinel lymph node specimens, make a note of any grossly visible blue dye. Make a note if multiple, matted, grossly involved lymph nodes are present. Measure the overall size of the matted lymph nodes.

Sentinel lymph nodes should be serially sectioned at 2-mm intervals perpendicular to the long axis and entirely submitted for microscopic examination.

Larger nonsentinel lymph nodes also need to be serially sectioned. Grossly negative lymph nodes need to be entirely submitted, whereas representative sections—including any areas suspicious for extracapsular invasion—are sufficient for grossly extensively involved and/or matted lymph nodes.

If multiple lymph nodes are present, submit each serially sectioned larger lymph node in its own cassette or multiple cassettes. Multiple smaller intact lymph nodes can be submitted in the same cassette. The number of lymph nodes in each cassette needs to be clearly designated.

If no lymph nodes are grossly identified, submit representative sections of adipose tissue.

V. Gross descriptions using paragraph system

Local excision, wide excision, and partial vulvectomy

Sample gross description

Received fresh, labeled with the patient's name, medical record number, and "right vulva" is a 4.6 x 3.2 cm elliptical portion of tan-brown skin excised to a depth of 0.5 cm. The specimen is oriented with a single stitch designated by the surgeon as 12 o'clock. There is a 2.5- x 2.2-cm tan-white irregular raised lesion coming to within 0.3 cm of the nearest 3 o'clock margin. Gross photographs are taken. The margin is inked black from 12-3-6 o'clock and inked blue from 6-9-12 o'clock, and the specimen is serially sectioned perpendicular to the long axis from 12 to 6 o'clock. The cut surfaces show no definitive abnormalities or gross invasion. The specimen is entirely submitted in nine cassettes, with the 12 o'clock tip in cassette #1 and the 6 o'clock tip in cassette #9.

Simple/total vulvectomy

Sample gross description

Received fresh, labeled with the patient's name, medical record number, and "vulva" is a 12- x 9-cm simple vulvectomy specimen excised to a depth of 1 cm, with a central circular defect measuring 2.2 x 1.5 cm. The overlying skin displays a 7- x 4.5-cm irregular, ill-defined tan-red, scaly area involving the clitoral hood and the bilateral labia majora anterior to the clitoris. The lesion comes to within 1 cm of the nearest right anterior (10-11 o'clock) skin margin. No other significant gross lesions are identified. Gross photographs are taken. The circumferential and deep margins are inked black, and the vaginal margin is inked blue. The specimen is pinned flat and fixed in formalin overnight. The cut surfaces show no definitive abnormalities or gross invasion. Sections are submitted per diagram as follows: cassettes 1-12: entire circumferential margin, en face; cassettes 13-15: entire vaginal margin, en face; cassettes 16-17: left anterior labium majus with lesion; cassettes 18-19: right anterior labium majus with lesion; cassette 20: clitoris with lesion; cassette 21: grossly normal left labium minus and majus; cassette 22: grossly normal right labium minus and majus.

Radical vulvectomy/anterior, posterior, or total

Sample gross description

Received fresh, labeled with the patient's name, medical record number, and "vulva with distal urethra and vagina" is a 14- x 10.5- cm radical vulvectomy specimen excised to a depth of 3 cm, with a central circular defect measuring 2.5 x 1.6 cm. Two surgical sutures are present: a blue suture marking the perineal body/inferior margin and a white suture marking the proximal urethral margin. The overlying skin measures 8 x 7 cm and displays a 4.4- x 3.7- cm firm tan-pink ulcerated lesion with irregular borders, involving the bilateral labia minora, right labium majus, and portion of the clitoris. The lesion comes to within 0.1 cm of the nearest right posterior (6-7 o'clock) skin margin. No gross urethral or vaginal involvement is identified. Gross photographs are taken. The circumferential and deep margins are inked black, and the vaginal margin is inked blue. The specimen is pinned flat and fixed in formalin overnight.

On sectioning, the lesion shows a tan-white cut surface with approximately 0.8-cm depth of invasion and comes to within 0.1 cm of the inked deep margin. The attached soft tissue is carefully sectioned to reveal no definitive lymph nodes or other gross lesions. Sections are submitted per diagram as follows: cassette 1: proximal urethra margin, en face; cassette 2: closest skin margin at 7 o'clock, perpendicular; cassettes 3-15: entire remaining circumferential margin, en face; cassettes 16-18: entire vaginal margin, en face; cassettes 19-23: lesion with maximum depth of invasion; cassette 24: additional sections of urethra.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

Sentinel lymph node biopsy

Received fresh, labeled with the patient's name, medical record number. and "sentinel lymph node right groin" are two fragments of yellow, lobulated, adipose tissue measuring 4.5 x 3 x 1 cm and 2.5 x 1.7 x 1 cm. Two lymph nodes are identified grossly within the adipose tissue, measuring 1.5 x 0.7 x 0.5 cm and 0.5 x 0.5 x 0.5 cm. The larger lymph node is serially sectioned to reveal a tan-blue cut surface and is entirely submitted in cassette 1. The smaller lymph node is bisected to show a tan-pink, grossly unremarkable cut surface and is entirely submitted in cassette 2.

Inguinal lymph node dissection

Received fresh, labeled with the patient's name, medical record number, and "left groin lymph nodes" is a 5.3 x 4.5 x 1.5 cm aggregate of adipose tissue, containing five tan-pink, rubbery lymph nodes, ranging from 0.4 cm to 2.5 cm in largest dimension. The three largest lymph nodes are serially sectioned. Cut sections of the largest lymph node show a 0.7-cm ill-defined tan-firm area, without definitive gross evidence of extracapsular extension. The smaller lymph nodes are grossly unremarkable. The lymph nodes are entirely submitted as follows: cassettes 1-2: largest, grossly suspicious lymph node, serially sectioned; cassettes 3 and 4: one serially sectioned lymph node in each cassette; cassette 5: two intact small lymph nodes.

VI. Common pathologic findings in the (index) specimen

Local excision, wide excision, and partial vulvectomy

Based on the indication, common pathologic findings in partial vulvectomy specimens include high-grade squamous intraepithelial lesion (HSIL) (VIN 2 or 3), dVIN, early-stage invasive squamous cell carcinoma, and

Paget disease. Occasionally, the lesion may have been removed entirely by the prior biopsy, and the excision specimen would only show scar without residual dysplasia or carcinoma.

Simple/total vulvectomy

Based on the indication, common pathologic findings in simple vulvectomy specimens include benign conditions (eg, extensive and/or symptomatic lichen sclerosus), preneoplastic lesions (HSIL/VIN 2-3, dVIN), Paget disease, or early stage invasive carcinoma.

Radical vulvectomy/anterior, posterior, or total

Radical vulvectomy is typically performed for clinically advanced (stage IB or higher) invasive carcinoma. Pathologic findings include invasive carcinoma, most commonly of squamous histologic subtype, often in the background of preneoplastic lesions (HSIL/VIN 2-3, dVIN), or lichen sclerosus. Approximately one third of invasive vulvar squamous carcinomas are associated with high-risk HPV infection ("warty"/basaloid squamous cell carcinoma), arise in the background of HSIL (VIN 2-3) and show diffuse, blocklike immunostaining with p16. The majority of vulvar squamous cell carcinomas, however, are HPV negative, are of the keratinizing subtype, may be associated with dVIN and/or lichen sclerosus, and may show abnormal p53 immunostaining pattern.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

One of the most important prognostic factors in vulvar squamous cell carcinoma is the presence of lymph node metastasis. The size of the metastatic focus should be carefully measured microscopically (Figure 34-8). According to the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, metastatic foci measuring not more than 0.2 mm should be considered isolated tumor cells and coded as "N0(i+)." If the size of metastatic focus measures more than 0.2 mm but less than 5 mm, the lymph node status is N1a (one or two positive lymph nodes) or N2a (three or more positive lymph nodes). Metastases measuring 5 mm or greater are considered N1b (one lymph node) or N2b (two or more lymph nodes). Extracapsular/extranodal extension, regardless of the size of metastatic focus, indicates worse prognosis and is considered N2c.

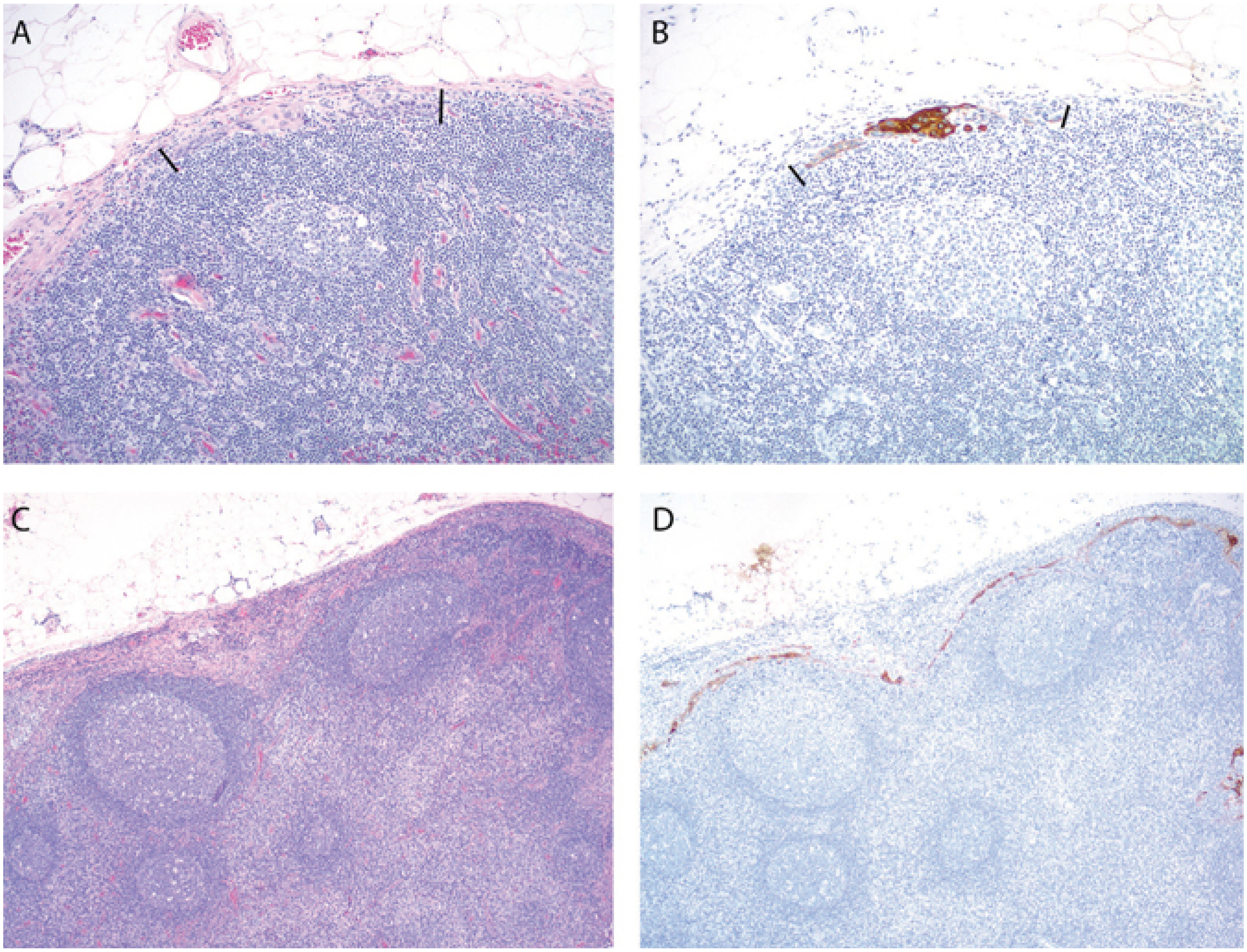

Figure 34-8. Inguinal sentinel lymph node with metastatic squamous cell carcinoma. The size of the largest continuous tumor focus should be measured. A, B. 0.5-mm metastatic focus (micrometastasis) is shown with hematoxylin-eosin (H&E) stain and CK AE1/AE3 immunostain. C, D. Indistinct subcapsular metastatic focus involves nearly the entire lymph node circumferentially. The largest continuous focus measured 7 mm on H&E and CK AE1/AE3 immunostain.

It should be noted that there are currently no uniform practice guidelines on ultrastaging sentinel lymph nodes in vulvar cancer. Prior studies in the literature proposed various combinations of deeper levels and CK immunohistochemistry.

VII. Common potential staging pitfalls and solutions

Local excision, wide excision, partial vulvectomy, and simple/total vulvectomy

When a partial vulvectomy is performed for high-grade dysplasia (VIN 2-3, dVIN), the specimen requires thorough gross sampling and microscopic examination to identify any potential invasive foci. In situ carcinoma involving irregular rete ridges or deep adnexal structures and suboptimal tissue orientation may mimic an invasive process (Figure 34-9). However, unlike true invasion, these foci show round, regular contours, and lack desmoplastic stromal reaction. Helpful microscopic features to identify early invasive squamous cell carcinoma include irregular contour of tumor cell clusters, adjacent stromal desmoplasia, and paradoxical maturation (Figure 34-10).

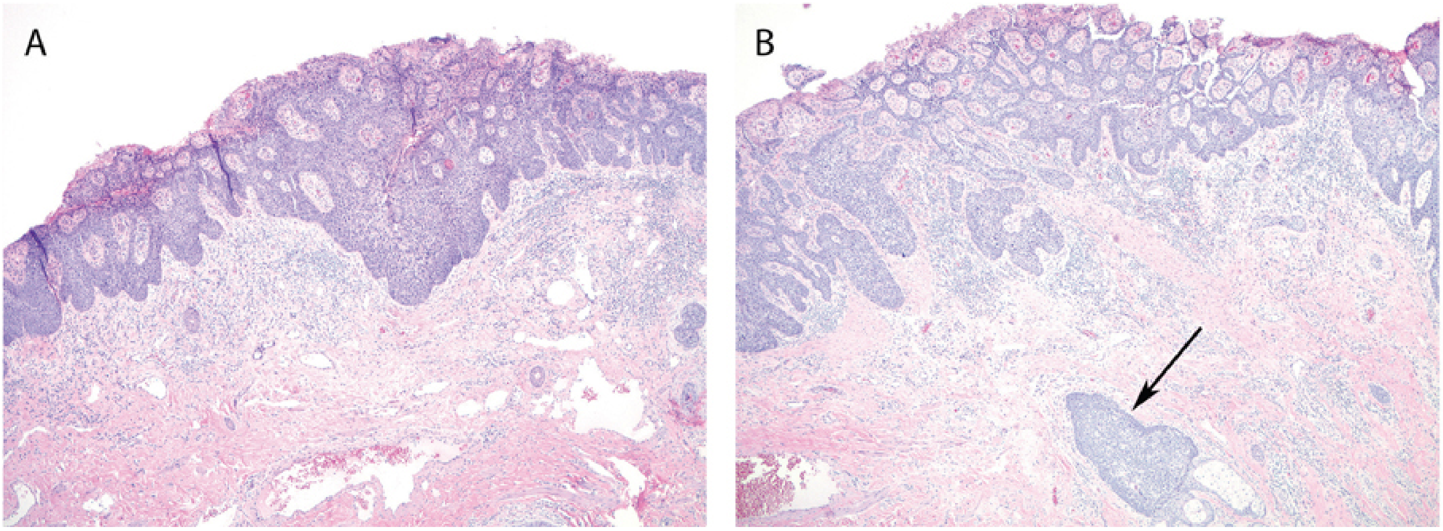

Figure 34-9. High-grade squamous intraepithelial lesion (vulvar intraepithelial neoplasia). Irregular, anastomosing rete ridges (A) and adnexal involvement (B, arrow) may mimic invasion.

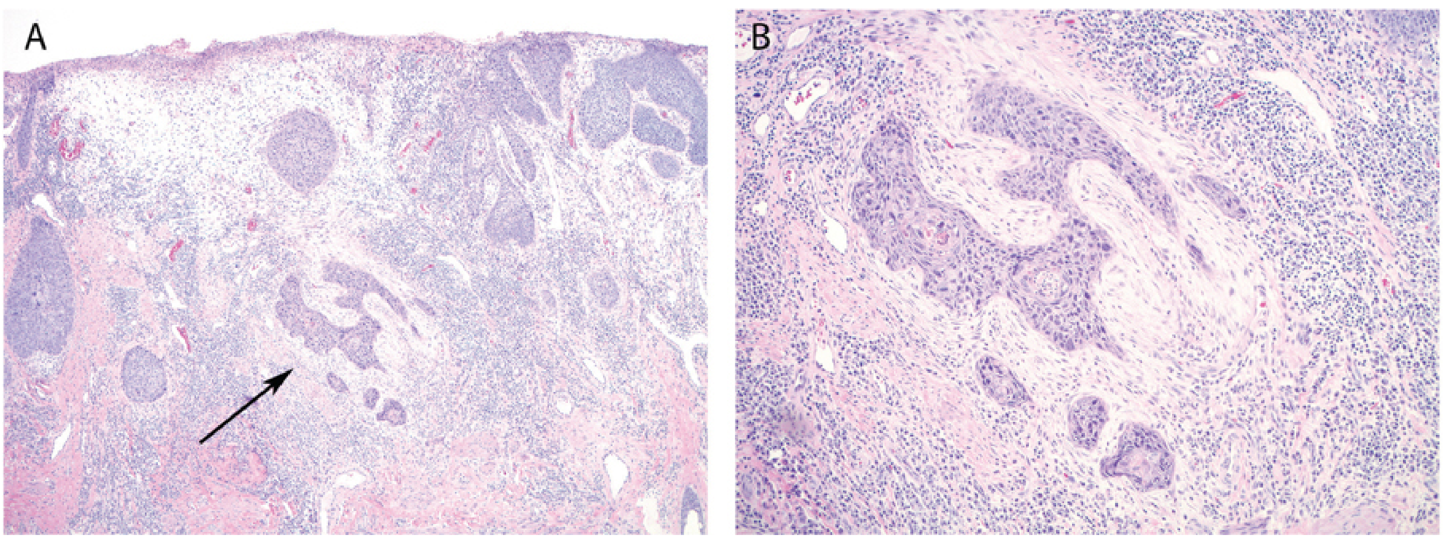

Figure 34-10. Superficially invasive vulvar squamous cell carcinoma. The invasive focus (A, arrow) is irregularly shaped and shows paradoxical maturation and stromal desmoplastic reaction (B).

If invasive carcinoma is present, the maximum horizontal extent has to be determined either on the basis of the microscopic measurement (for small foci) or estimated on the basis of the combination of gross and microscopic findings (for larger foci spanning multiple sections). Precise measurement of depth of stromal invasion is crucial for staging of early stage vulvar carcinomas. Depth of invasion should be measured microscopically from the epithelial-stromal junction of the adjacent, most superficial, dermal papilla to the deepest point of invasion (Figure 34-11). Depth of invasion should not be confused by tumor thickness (measured from the surface of the tumor or from the bottom of the granular layer to the deepest point of invasion), because tumor thickness is not used for staging purposes.

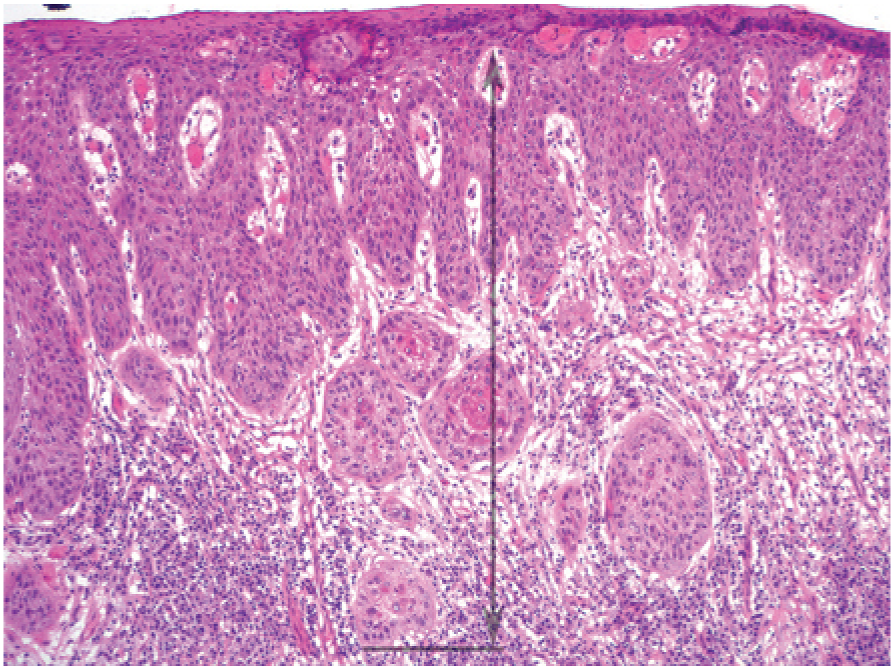

Figure 34-11. Superficially invasive vulvar squamous cell carcinoma. Depth of invasion should be measured microscopically from the epithelial-stromal junction of the adjacent, most superficial, dermal papilla to the deepest point of invasion (arrow).

If Paget disease is identified, immunohistochemical stains may help rule out secondary spread from a urothelial or anorectal primary. In addition, immunohistochemical stains (eg, CK7, CAM 5.2, or CEA) may also be helpful in identifying foci of invasion and assessing the margin status.

Although presence of lymphovascular invasion (LVI) does not affect the tumor stage, it constitutes an important prognostic parameter and should be included in the final pathology report. Endothelial immunohistochemical markers can be used in difficult cases to distinguish between tissue retraction artifact and LVI (Figure 34-12).

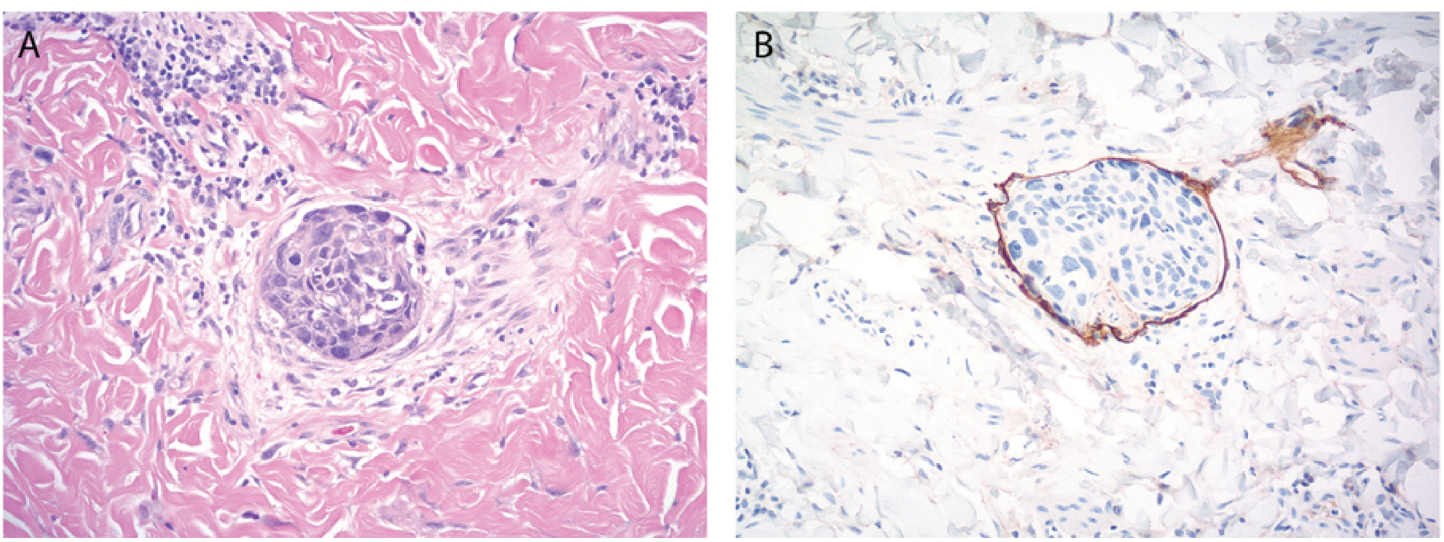

Figure 34-12. Lymphovascular invasion by squamous cell carcinoma (A). D2-40 immunostain (B) is helpful in confirming tumor within a lymphatic space and distinguishing it from tissue retraction artifact.

Radical vulvectomy/anterior, posterior, or total

The size of the invasive carcinoma in a radical vulvectomy specimen needs to be measured carefully. It is often difficult to clearly distinguish the in situ and invasive tumor components on gross examination; therefore,

the final invasive tumor size should be based on correlation between microscopic and gross findings. Presence of multifocal invasive disease should be noted. Depth of invasion should be measured microscopically from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion (Figure 34-11). Depth of invasion should not be confused by tumor thickness (measured from the surface of the tumor or from the bottom of the granular layer to the deepest point of invasion), because tumor thickness is not used for staging purposes.

Although presence of LVI does not affect the tumor stage, it constitutes an important prognostic parameter and should be included in the final pathology report. Endothelial immunohistochemical markers can be used in difficult cases to distinguish between tissue retraction artifact and LVI (Figure 34-12).

Involvement of adjacent perineal structures (distal third of urethra and/or vagina and/or anus) should be carefully assessed and confirmed by microscopic examination because it increases the tumor stage to pT2, regardless of tumor size. A precise grossing diagram can be invaluable in guiding this assessment.

Regional lymph nodes: sentinel lymph node biopsy and node dissection

Only inguinal and femoral lymph nodes are considered regional lymph nodes for vulvar carcinoma. Tumor in pelvic and/or paraaortic lymph nodes is regarded as a distant metastasis.

Tumor within a lymphovascular space outside of the lymph node capsule should not be regarded as a metastatic focus, nor should it be considered extracapsular extension or included in the size measurement if an intranodal metastatic focus is present. Extranodal extension may be difficult to identify if the metastatic tumor has a pushing border and/or is surrounded by an extensive fibrous reaction (“pseudocapsule”) (Figure 34-13). It may be helpful to evaluate the lymph node contour in these cases: tumor foci bulging out of the round node contour favor extracapsular spread. Microscopic assessment of extracapsular spread may be compromised if the adipose tissue surrounding the lymph node has been dissected off, partially or entirely, during grossing (Figure 34-14).

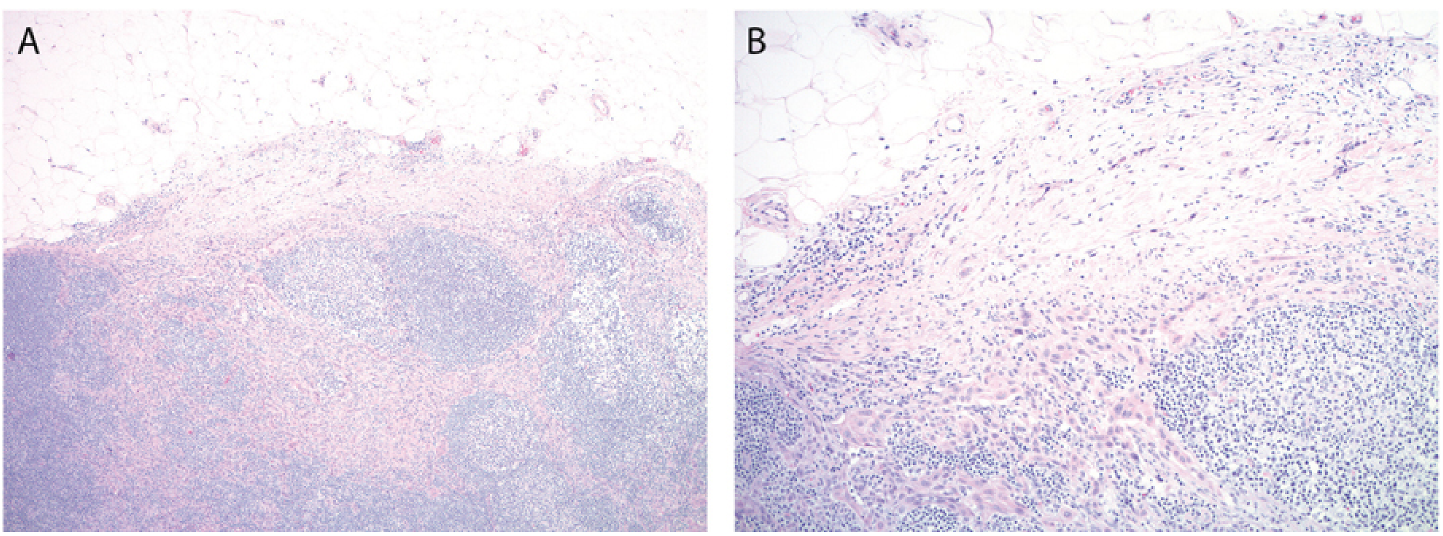

Figure 34-13. Inguinal lymph node metastasis with focal extracapsular extension (A, B). The tumor elicits dense desmoplastic stromal response (“pseudocapsule”), mimicking a thickened lymph node capsule.

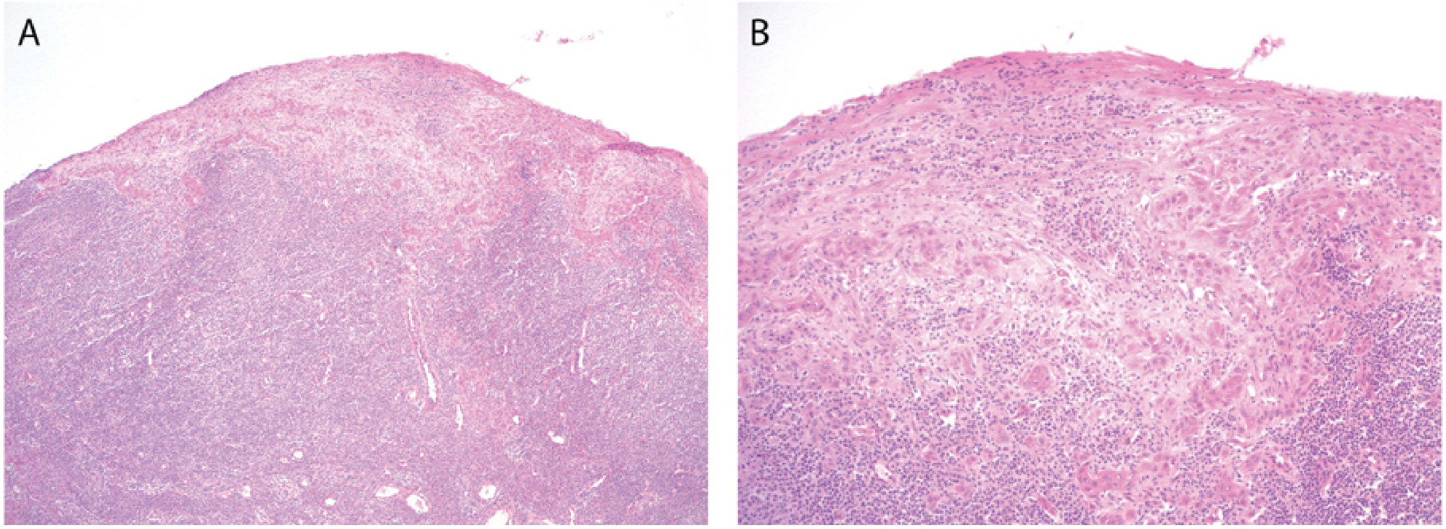

Figure 34-14. Frozen section of an inguinal lymph node metastasis (A, B). Part of the lymph node capsule and the adjacent adipose tissue was dissected off, limiting the evaluation of extracapsular extension.

The distinction between extensive extracapsular extension (N2c) versus "fixed" lymph node metastasis (N3) may be difficult to make on the basis of pathology evaluation alone; however, large matted positive lymph nodes would fall within this category.

VIII. What to include in the pathology report

Local excision, wide excision, and partial vulvectomy

The final pathology report of a local excision/partial vulvectomy must include the following:

1. Site/laterality and procedure performed
2. Presence of in situ or invasive carcinoma
   a. For in situ carcinoma, distinction between a high-risk human papillomavirus (HPV)–driven (HSIL/VIN2-3) and an HPV-negative (dVIN) process should be made, if possible. Immunohistochemical stains for p16 and p53 are often helpful in this setting.
   b. Paget disease
3. Histologic subtype and grade of invasive carcinoma
4. Tumor focality (unifocal/multifocal)
5. Maximum horizontal extent of invasive carcinoma
6. Maximum depth of stromal invasion
7. Presence or absence of LVI
8. Margin status (circumferential and deep margins)
   a. If negative, indicate the distance to the closest margin.
   b. Indicate the location of the closest or positive margin.

Samples for final diagnosis and synoptic report

Final diagnosis

Vulva, right, partial vulvectomy

- Invasive squamous cell carcinoma, moderately differentiated
- Maximum horizontal extent: 8 mm
- Maximum depth of invasion: 3 mm
- LVI is present (confirmed by D2-40 immunostain)
- Background HSIL (VIN 3)
- All margins are negative for high-grade dysplasia and invasive carcinoma
- AJCC stage (8th ed): pT1b Nx, at least stage IB

Synoptic report

Specimen: Vulva
Procedure: Partial vulvectomy
Tumor type: Invasive carcinoma
Histologic type: Squamous
Histologic grade: Moderately differentiated
Tumor size:
Greatest dimension: 8 mm; additional dimension: 7 mm
Maximum depth of stromal invasion: 3 mm
Other tissue/organ involvement: Not applicable
Margins: Negative; invasive carcinoma is 5 mm away from the nearest 3 o'clock margin
LVI: Present
Associated epithelial lesions: HSIL (VIN 3)
Pathologic staging (pTNM) primary tumor (pT): pT1b
Regional lymph nodes (pN): pNx
Number of lymph nodes examined: 0
Distant metastasis (pM): N/A

Simple/total vulvectomy

The final pathology report of a simple/total vulvectomy must include the following:

1. Site and procedure performed
2. Presence of in situ or invasive carcinoma
   a. For in situ carcinoma, distinction between an HPV-driven (HSIL/VIN 2-3) and an HPV-negative (dVIN) process should be made, if possible. Immunohistochemical stains for p16 and p53 are often helpful in this setting.
   b. Paget disease
3. Histologic subtype and grade of invasive carcinoma
4. Tumor focality (unifocal/multifocal)
   a. Location of tumor, anatomic structures involved
5. Maximum horizontal extent of invasive carcinoma
6. Maximum depth of stromal invasion
7. Presence or absence of LVI
8. Margin status (circumferential, vaginal, and deep margins)
   a. If negative, indicate the distance to the closest margin.
   b. Indicate the location of the closest or positive margin.

Samples for final diagnosis and synoptic report

Final diagnosis

Vulva, simple vulvectomy
- Primary vulvar Paget disease, involving clitoris and bilateral labia majora anteriorly
- Tumor size: Approximately 7 cm in largest horizontal extent (estimated based on gross assessment)
- No invasion is identified (confirmed by CAM 5.2 immunostain).
- Right lateral skin margins are positive for Paget disease (at 10-11 o'clock position).
- All other margins, including vaginal margin, are negative for Paget disease."

Synoptic report

Specimen: Vulva
Procedure: Simple vulvectomy
Tumor type: Paget disease
Size: 7 x 4.5 cm
Sites involved: Bilateral labia majora, clitoris
Stromal invasion: Not identified
Margins: Positive anterior right skin margin (10-11 o'clock position)

Pathologic staging (pTNM): N/A

Radical vulvectomy/anterior, posterior, or total

The final pathology report of a radical vulvectomy has to include the following:

1. Site and procedure performed
2. Presence of invasive carcinoma
3. Histologic subtype and grade of invasive carcinoma
   a. Immunohistochemical stains for p16 and p53 may provide helpful information regarding pathogenesis and prognosis.
4. Tumor focality (unifocal/multifocal)
   a. Location of tumor, anatomical structures involved
5. Maximum horizontal extent of invasive carcinoma
6. Maximum depth of stromal invasion
7. Presence or absence of LVI
8. Margin status (circumferential, vaginal, urethral, anal, and deep margins)
   a. If negative, indicate the distance to the closest margin.
   b. Indicate the location of the closest or positive margin.
9. Presence of background lesions: In situ carcinoma (HSIL or dVIN) or lichen sclerosus.
10. Lymph node status (if sentinel or nonsentinel lymphadenectomy was performed) – see below.

Samples for final diagnosis and synoptic report

Final diagnosis

Vulva, distal urethra and vagina, and bilateral inguinal sentinel lymph nodes; radical total vulvectomy and bilateral sentinel lymph node biopsy

- Invasive squamous cell carcinoma, poorly differentiated
- Maximum horizontal extent: 4.4 cm
- Maximum depth of invasion: 0.8 cm
- Tumor involves right labium majus, bilateral labia minora, and clitoris
- LVI is present, extensive
- Urethral involvement: Present
- Vaginal involvement: Not identified
- Background HSIL (VIN 3)
- All margins—including urethral, vaginal, deep and circumferential skin margins—are negative for high-grade dysplasia and invasive carcinoma.
- One of two right inguinal sentinel lymph nodes positive for metastatic carcinoma (1/2)
- Size of largest metastatic focus: 4 mm
- Extracapsular extension is not identified.
- One left inguinal sentinel lymph node, negative for carcinoma (0/1)
- AJCC stage (8th ed): pT2 N1a, stage IIIA

Synoptic report

Specimen: Vulva

Procedure: Radical total vulvectomy

Tumor type: Invasive carcinoma

Histologic type: Squamous

Histologic grade: Poorly differentiated

Tumor size: Greatest dimension: 4.4 cm; additional dimension: 3.7 cm

Maximum depth of stromal invasion: 8 mm

Other tissue/organ involvement: Urethra

Margins: Negative; invasive carcinoma is 1 cm away from the nearest right posterior skin margin

LVI: Present

Associated epithelial lesions: HSIL (VIN 3)

Number of lymph nodes examined: 3
Number of lymph nodes involved: 1
Size of largest metastatic focus: 4 mm
Extracapsular extension: Absent
Pathologic staging (pTNM) primary tumor (pT): pT2
Regional lymph nodes (pN): pN1a
Distant metastasis (pM): N/A

Regional lymph nodes: sentinel lymph node biopsy and node dissection

The final pathology report of a sentinel lymph node biopsy or lymph node dissection for vulvar squamous cell carcinoma must include the following:

1. Anatomical site and laterality
2. Procedure performed
   a. Sentinel lymph node biopsy versus node dissection
3. Total number of lymph nodes examined
4. Number of lymph nodes involved by metastatic carcinoma
5. Size of metastatic foci
6. Presence or absence of extracapsular extension
   a. If present, it may be helpful to quantify the extent—focal versus extensive
7. For sentinel lymph nodes: Include a note to describe methods used for ultrastaging, if any (eg, levels, CK immunostains, etc).

Samples for final diagnosis and synoptic report—see above (included in final diagnosis and synoptic report for radical vulvectomy).

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35. Larynx and Pharynx

Li Liang, MD, PhD; Diana Bell, MD

I. Indications for laryngectomy and pharyngolaryngectomy

Total laryngectomy is most often performed to treat invasive squamous cell carcinoma, especially for patients with recurrent tumors after nonsurgical treatments, such as radiotherapy and/or chemotherapy (see Figures 35-1 through 35-2). Laryngectomy can also be performed to treat patients with mesenchymal tumors or nonfunctional larynges. Cartilage tumor (ie, chondrosarcoma) is the most common mesenchymal tumor in the larynx (see Figure 35-3).

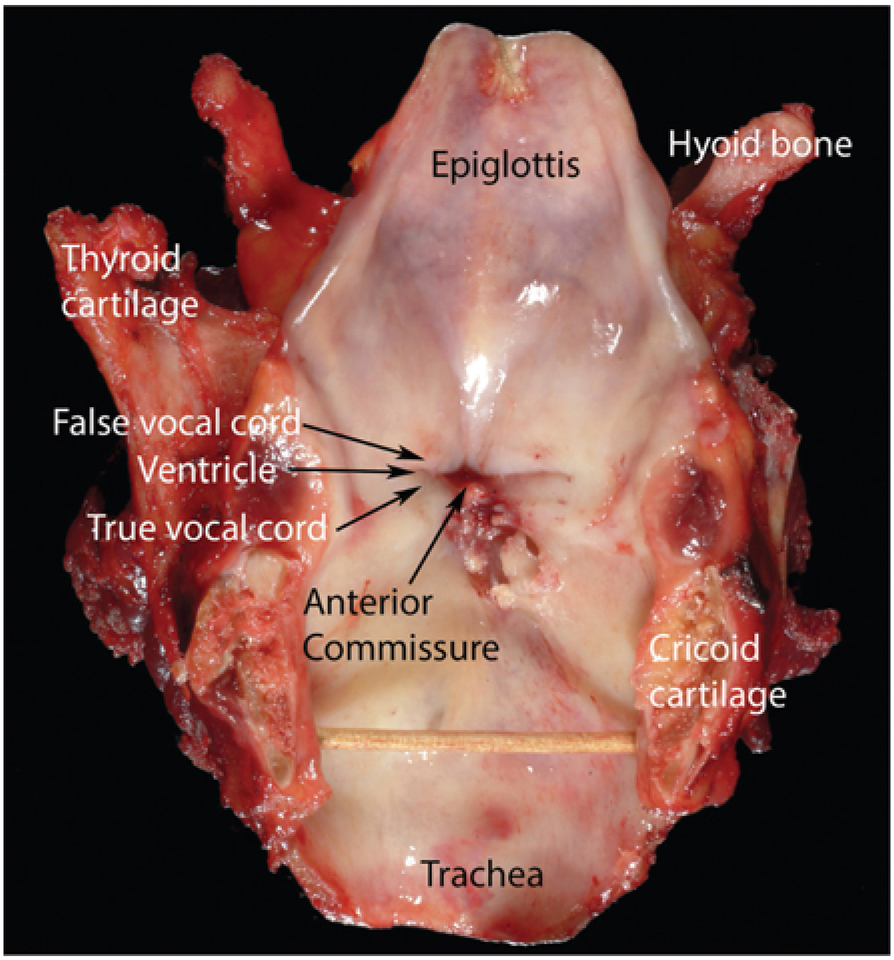

Figure 35-1. Laryngectomy specimen shows invasive squamous cell carcinoma involving the glottis and subglottis.

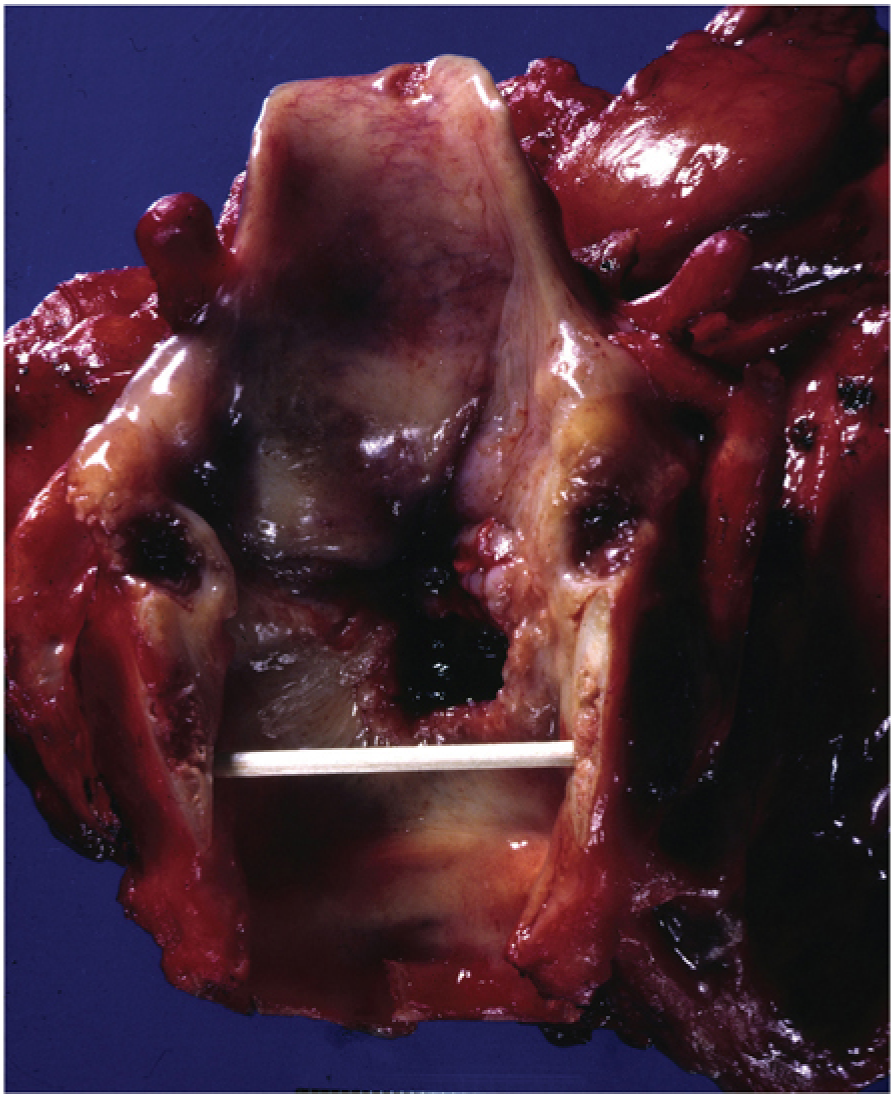

Figure 35-2. Laryngectomy specimen shows transglottic squamous cell carcinoma.

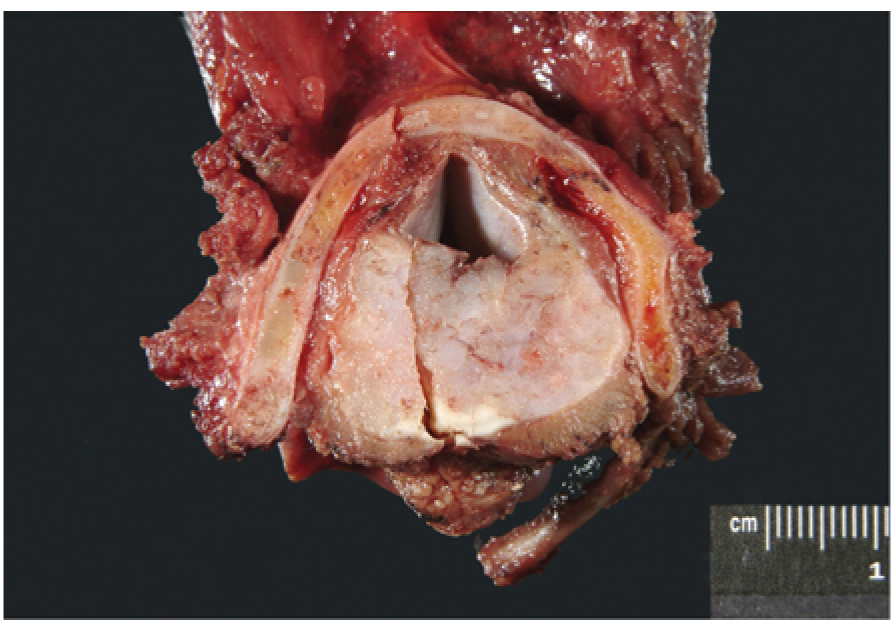

Figure 35-3. Gross photo of laryngeal chondrosarcoma.

Pharyngolaryngectomy is typically performed for hypopharyngeal cancers, which are less common than laryngeal cancers. The hypopharynx is the inferior portion of the pharynx, between the oropharynx and the esophagus. It is located posterior to the larynx and composed of the posterior pharyngeal wall, piriform sinus (Figure 35-4), and postcricoid area. Determining the primary site of the tumor and the relationship between the tumor and adjacent structures (ie, esophagus, thyroid gland, thyroid/cricoid/arytenoid cartilages) is important during gross examination. This type of specimen is usually handled like a laryngectomy specimen.

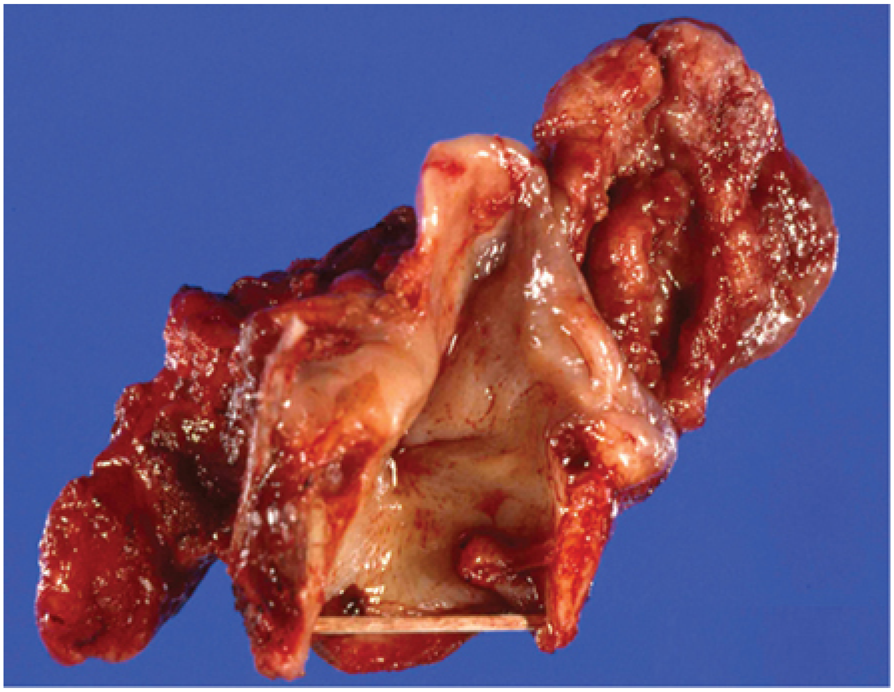

Figure 35-4. Gross photo of squamous cell carcinoma of the pyriform sinus.

II. What do we expect to see in laryngectomy specimens?

The larynx is divided into three parts: supraglottis, glottis, and subglottis.[1] Glottic cancers are most common, followed by supraglottic cancers; subglottic cancers are least common. The supraglottis consists of the epiglottis, aryepiglottic folds, arytenoids, false cords, and ventricles. The superior boundary of the supraglottis is the free edge of the epiglottis and aryepiglottic fold. The glottis is composed of true vocal cord and anterior and posterior commissure. The superior boundary of the glottis (also the inferior boundary of the supraglottis) is the horizontal through the apex of the laryngeal ventricle. The inferior boundary of the glottis (also the superior boundary of subglottis) is 1 cm below the free edge of true vocal cord. The inferior boundary of the subglottis is the inferior margin of the cricoid cartilage. The pre-epiglottic space is an inverted pyramid-shaped space: the superior boundary is the hyoepiglottic ligament; the anterior boundary is the thyrohyoid membrane/ligament and thyroid cartilage; the posterior boundary is the epiglottis and thyroepiglottic ligament.

The head and neck chapters cover the common head and neck resection specimens, including laryngectomy, pharyngolaryngectomy, glossectomy/oral cavity resection, transoral robotic surgery (TORS) of base of tongue and tonsil, mandibulectomy, maxillectomy, parotidectomy, auriculectomy, and left neck lymph node dissection. Owing to the complex anatomic structures, head and neck specimens can be difficult to handle. It is important to not only make the correct diagnosis, but also to provide information regarding the extent of tumor growth, anatomic structures involved by the tumor, resection margin status and to indicate whether perineural, vascular, or bone invasion is present.

The most common pathologic finding in head and neck specimens is squamous cell carcinoma. However, laryngectomy may also be performed for mesenchymal tumors and nonneoplastic conditions (ie, nonfunctional larynges).

Laryngectomy includes total and partial laryngectomy (see Table 35-1 for a summary of the procedures performed on the larynx). A total laryngectomy specimen is not only composed of the laryngeal structures, but may also contain adjacent structures, such as thyroid gland, pharynx (ie, pyriform sinus or lateral pharyngeal wall), tongue, hyoid bone, strap muscles, skin, and stoma site (see Figure 35-1). It is always helpful to review the operative notes and imaging findings before grossing the specimen.

Table 35-1. Surgical Procedures Performed on the Larynx

Partial laryngectomy	A. Cordectomy via laryngofissure B. Vertical or frontolateral partial laryngectomy C. Horizontal partial laryngectomy • Supraglottic procedure • Supracricoid procedure D. Combinations and extensions of A, B, and C with or without involvement of the ventricles, ventricular bands, aryepiglottic folds, and juxtaposed portion of medial wall of pyriform sinus
Total laryngectomy	A. Narrow field laryngectomy B. Wide field laryngectomy

III. Dissection techniques: step-by-step description

1. Review the outer surface of the specimen carefully and document the measurements.[2] It is important to examine both the anterior and posterior aspects of the specimen. The tumor may extend to extralaryngeal structures, such as trachea, thyroid, esophagus, strap muscles, or deep extrinsic muscle of tongue.

2. Submit the resection margins, including bilateral superior mucosal margins and tracheal margin. In addition, pharyngeal, tongue, and anterior soft tissue margins can also be submitted if grossly suspicious. The strap muscle may retract, which makes it difficult to assess the true margin status. Discussion with the surgeon may be needed if the tumor is grossly abutting the anterior soft tissue margin. Intraoperative evaluation of the above margins may be requested by the surgeon. In addition, the surgeon may also submit separate resection margins for intraoperative evaluation and/or permanent review.

3. Open the larynx along the posterior midline after palpating the tumor by inserting a finger into the laryngeal lumen.

4. Describe the gross features of the tumor (see Table 35-2).[3,4]

Table 35-2. The Key Points for Gross Description of Laryngeal Carcinoma	
Category	**Key points**
Gross features	Exophytic or ulcerated; tumor necrosis.
Tumor site	Supraglottic, glottic (extending up to 1 cm below the true vocal cord), or subglottic.
Laterality	Check if the tumor involves the anterior commissure and/or crosses the midline.
Tumor size	The tumor should be measured three dimensionally on cross-sections. Surface ulceration or exophytic tumor may only be "the tip of the iceberg," and the actual tumor size tends to be much bigger and should be remeasured on cross-sections.
Distance from the tumor to the resection margins	Measure the distance of the tumor to all the margins.
Cartilage involvement	Document if thyroid cartilage, cricoid, and arytenoid cartilages are grossly involved by the tumor.
Adjacent anatomic structure	Document whether the tumor grossly involves the thyroid gland, hypopharynx, tongue, anterior strap muscle, and skin/stoma site.

5. Peel off the mucosa from the underlying cartilage. Submit a longitudinal section (superior to inferior) of the laryngeal mucosa with tumor, which can be bisected or trisected to fit into the cassettes. Submit a longitudinal section of laryngeal mucosa on the opposite side. A midline section may also be submitted if the tumor is grossly abutting the midline. If the patient has undergone preoperative chemoradiotherapy, sometimes no tumor can be grossly identified, and it is important to adequately sample the scar/fibrotic area to rule out microscopic residual tumor.

6. Submit sections of tumor with adjacent anatomy structures, including the hypopharynx, base of tongue, thyroid, and so forth. The attached soft tissue should be examined carefully. Submit any suspicious area and all the lymph nodes identified.

7. Sections of the cartilage are usually submitted after decalcification. If the cartilage is not calcified or completely replaced by tumor, it is also possible to submit sections of the cartilage without decalcification.

IV. Gross description of laryngectomy specimen

Total laryngectomy and right thyroidectomy—A total laryngectomy specimen with attached perilaryngeal soft tissue (9.0 x 8.0 x 6.5 cm overall) and right thyroid lobe (3.0 x 2.5 x 1.5 cm) was submitted. The larynx is opened to reveal a glottis/subglottis ulcerated area, 1.5 cm away from the tracheal margin. Mucosal margins are shaved off. The specimen is sectioned to reveal a tan ill-defined tumor underlying the ulcerated area (measuring 3.0 x 2.5 x 2.0 cm). The tumor involves bilateral glottis and subglottis (extending 2.0 cm below the vocal cord). The tumor grossly invades the thyroid cartilage. The thyroid parenchyma is grossly unremarkable. Three possible lymph nodes are identified (up to 1.0 cm in greatest dimension).

Section code

A1: Right mucosal margin

A2: Left mucosal margin

A3: Tracheal margin
A4: Anterior soft tissue
A5-A6: Left glottis and subglottis with the tumor and underlying cartilage
A7-A8: Right glottis and subglottis with the tumor
A9: Thyroid parenchyma
A10: Three possible lymph nodes

V. Common potential staging pitfalls and solutions

1. Extralaryngeal extension

Identification of extralaryngeal extension is critical to avoid understaging of laryngeal carcinoma. Extralaryngeal extension is defined as tumor invading into cricoid cartilage, trachea, thyroid, esophagus, strap muscles, deep extrinsic muscle of tongue, and so forth.

2. Clinical and radiologic correlation

Pathologic findings should always be correlated with clinical and radiologic findings. For example, if extralaryngeal extension is suspected by the radiologist while not documented in the gross description, the specimen should be reexamined. This also applies whenever there are any other discrepancies (eg, tumor size). Ideally, imaging studies should always be reviewed by the pathologist ahead of time (ie, the day before the surgery is scheduled). Moreover, if there is any discrepancy between clinical impression and pathology findings, the case should be discussed with the surgeon.

VI. What to include in the pathology report

1. MD Anderson Cancer Center Diagnosis Template

The following is an example of a pathology report for a resection specimen for squamous cell carcinoma, which includes information about gross features, tumor size, depth of invasion, tumor board, perineural invasion, lymphovascular invasion, and bone/cartilage invasion:

Invasive squamous carcinoma—moderately differentiated
Tumor features
  Gross: Ulcerating
  Size: 3.5 cm in largest dimension
  Invasion: Present, depth 1.8 cm
  Tumor border: Infiltrative with thick cords >4 cells (or with thin cords <4 cells)
  Perineural invasion: Present, focal
  Vascular invasion: Present, in submucosal lymphatics
  Bone/cartilage invasion: Cartilage invasion present

2. In addition to the above MD Anderson Cancer Center Diagnosis Template, a cancer protocol checklist should also be included in the pathology report. Although it is slightly variable at different tumor sites, the following information should generally be included in the pathology report of a head and neck specimen. Please also refer to the American Joint Committee on Cancer staging manual (8th ed)[5] and the College of American Pathologists (CAP) website (www.cap.org) for more information. Here is an example of the CAP cancer protocol:

LARYNX (SUPRAGLOTTIS, GLOTTIS, SUBGLOTTIS):
Procedure: Total laryngectomy
Tumor Site: Larynx, supraglottis
Transglottic Extension: Not identified
Tumor Laterality: Left
Tumor Focality: Unifocal
Tumor Size:
  Greatest dimension (centimeters): 3.0 cm
  Additional dimensions (centimeters): 2.0 x 1.5 cm

Histologic Type: Squamous cell carcinoma, conventional (keratinizing)
Histologic Grade: G2: Moderately differentiated
Tumor Extension: Tumor involves mucosa of base of tongue
Margins:
Uninvolved by invasive tumor
Distance from closest margin (millimeters): 20 mm
Specify location of closest margin: left superior mucosal margin
Uninvolved by high-grade dysplasia/in situ disease:
Distance from closest margin (millimeters): 15 mm
Specify location of closest margin: left superior mucosal margin
Lymphovascular Invasion: Present
Perineural Invasion: Not identified
Regional Lymph Nodes:
Number of Lymph Nodes Involved: 1
Number of Lymph Nodes Examined: 15
Laterality of Lymph Nodes Involved: Ipsilateral
Size of Largest Metastatic Deposit (centimeters): 0.8 cm
Extranodal Extension (ENE): Present, ENEmi (≤2 mm)
Pathologic Stage Classification (pTNM, AJCC 8th ed): ypT2 N2a M(n/a)

3. Other information that is usually included in the pathology report includes a brief clinical history and gross description. In addition, the pathologist may select tissue blocks that contain tumor and normal control tissue to be used for potential future biomarker testing.

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36. Lip, Oral Cavity, and Base of Tongue/Tonsil

Li Liang, MD, PhD; Diana Bell, MD

I. Indication for oral cavity resection

The most common pathologic finding in oral cavity resection specimens is squamous cell carcinoma. However, various tumor types can be seen, such as odontogenic, salivary gland, and mesenchymal tumors, as well as mucosal melanoma and lymphoma. In addition, secondary tumors are not uncommon in head and neck resection specimens. Skin tumors (eg, squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, adnexal neoplasm, and melanoma), and brain tumors (eg, meningioma) can either directly extend to or metastasize to head and neck structures. Distant metastasis (eg, of breast, lung, kidney, prostate, or gynecologic origin) can also been seen. Oral cavity resection may also be performed for nonneoplastic conditions, such as infectious disease, osteoradionecrosis, and bisphosphonate-related osteonecrosis.

II. What do we expect to see in oral cavity resection specimens?

Glossectomy and floor-of-mouth resection are typically performed for non-human papillomavirus (HPV)-associated squamous cell carcinoma and, less commonly, salivary gland or mesenchymal tumors (see Figures 36-1 and 36-2).

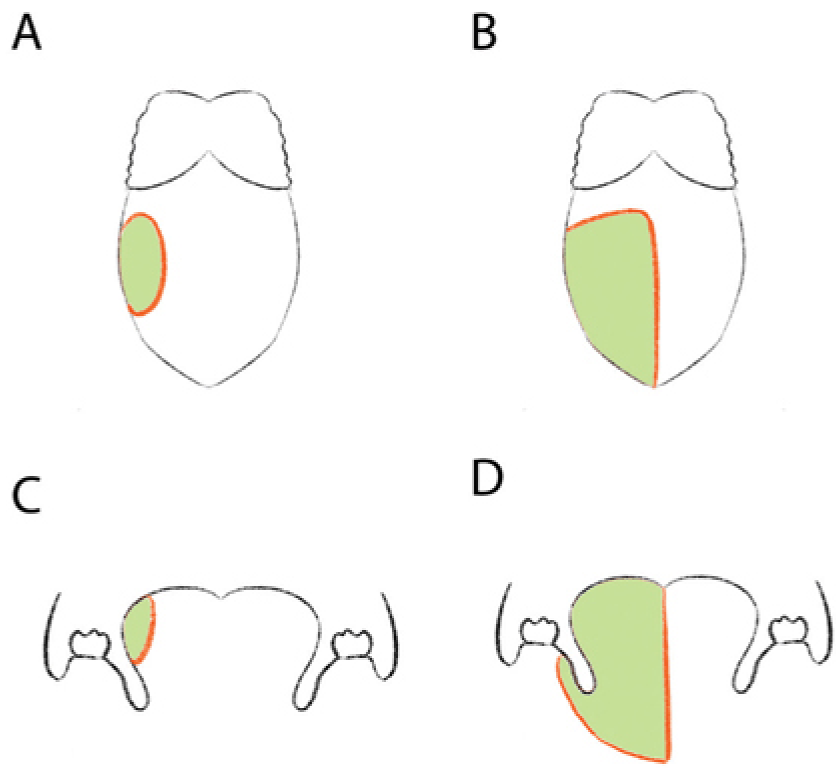

Figure 36-1. Diagrams of glossectomy specimens. A, C. Partial glossectomy. B, D. Glossectomy specimen including a portion of the floor of the mouth. The resection margins are highlighted in orange.

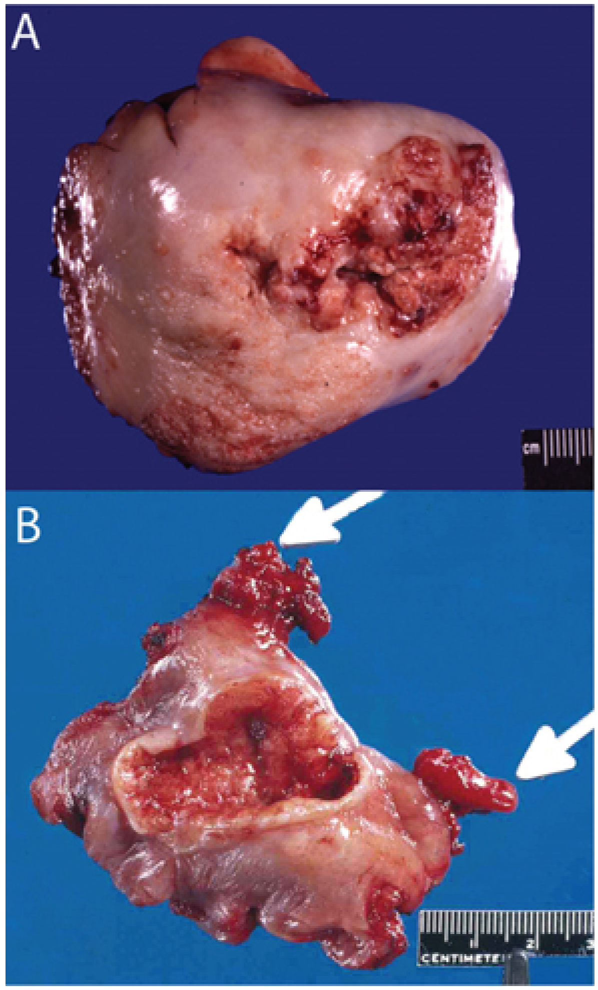

Figure 36-2. Gross photos of specimens from the oral cavity. A. A glossectomy specimen with an ulcerated tumor. B. A mucosal lip resection specimen.

Transoral robotic surgery (TORS) is a minimally invasive procedure for treating early-stage oropharyngeal cancers, such as the base of the tongue and tonsillar cancers (see Figure 36-3). TORS is associated with less morbidity and better outcome in a selected group of patients. However, TORS is also a challenging procedure owing to the limited surgical field and complex anatomical structures. Intraoperative evaluation plays a crucial role in assessing the margin status of TORS specimens.

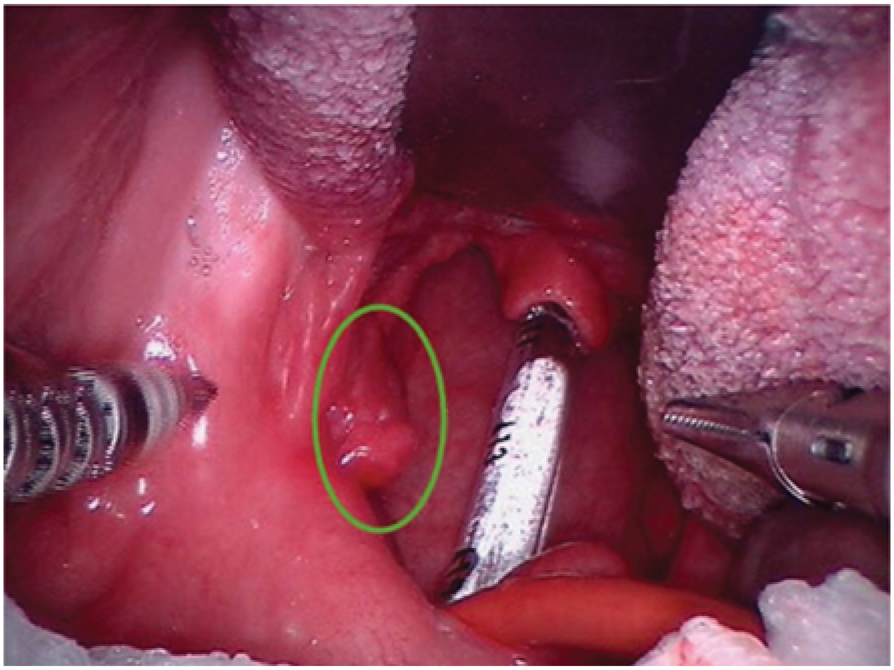

Figure 36-3. Left tonsil tumor (green circle) to be removed by minimally invasive transoral robotic surgery (TORS). (Image courtesy of Neil Gross, MD.)

Mandibulectomy is most commonly performed for invasive squamous cell carcinoma but also for mesenchymal neoplasms, such as osteosarcoma, Ewing sarcoma, peripheral nerve sheath tumor, and so forth.

There are several different types of mandibulectomy specimens, including hemimandibulectomy, segmental mandibulectomy, and marginal mandibulectomy (see Figure 36-4). Hemimandibulectomy is resection of half of the mandible, including the ramus, angle, and mandibular body. Segmental mandibulectomy is resection of a portion of full-thickness mandible with two resection margins, and the condyle is preserved.[1] Marginal mandibulectomy is partial-thickness resection of the mandible.[1] Being familiar with different types of mandibulectomy specimen is important when assessing the resection margins. A composite resection specimen may also contain floor of the mouth, tongue, buccal mucosa, skin/lip, or a portion of the maxilla.

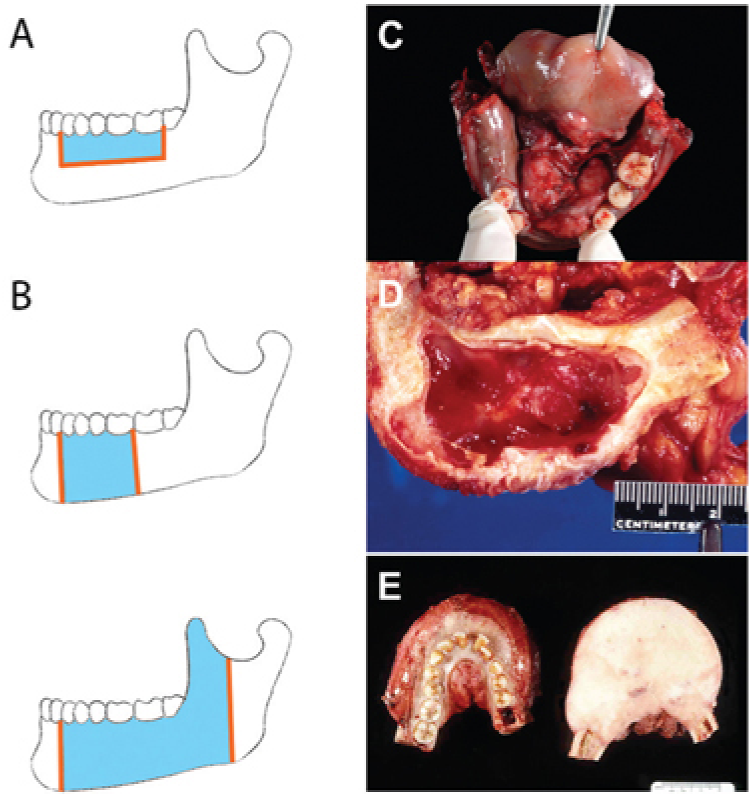

Figure 36-4. Diagram of marginal mandibulectomy (A) and segmental mandibulectomy (B). The margins of resection are highlighted in orange. C. Composite resection with almost angle-to-angle mandibulectomy and near-total glossectomy, which showed a large tumor in the floor of mouth. D. Segmental mandibulectomy for a central mucoepidermoid carcinoma. E. Angle-to-angle mandibulectomy for osteosarcoma.

III. Dissection techniques: step-by-step

Glossectomy/floor-of-mouth resection/TORS of base of tongue and tonsil

1. Review the specimen and draw a diagram, if needed. The tumor site should be documented accurately (ie, lateral border of tongue, upper/lower gingiva, floor of mouth, buccal mucosa, retromolar trigone, external upper/lower lip, mucosa of upper/lower lip, commissure of lip, etc). It is not uncommon to have multiple primary tumors, and each tumor should be described separately.

2. Measure the distance of the tumor to the mucosal and deep margins. A 5-mm clear margin is considered adequate. The lateral/medial margins may be inked for orientation under the microscope.

3. Circumferential mucosal margins are usually submitted en face, and the deep margin is submitted perpendicularly. Submit sections with the tumor and adjacent mucosa sequentially. Alternatively, a small specimen can also be bread-loafed and entirely submitted.

Mandibulectomy

1. Review the specimen and document the measurements. Loose teeth are indicative of possible bone invasion and should be described. If the lip is present, it is important to take note whether it is full thickness (including both the skin and mucosa).

2. Describe the gross features of the tumor (ulcerative or exophytic, color, size, consistency, unifocal or multifocal, distance to margins). Also, document if any other abnormalities (eg, leukoplakia) are present.

3. Submit the resection margins, including buccal mucosal and lingual mucosal margins. Deep soft-tissue margins can be submitted if grossly suspicious. If the skin or lip is present, also submit the skin and lip margins. The inferior alveolar nerve is a branch of the mandibular nerve (the largest division of the trigeminal nerve). The inferior alveolar nerve enters the mandibular foramen and travels within the mandibular canal.[1] The tumor can travel along the inferior alveolar nerve and reach the resection margins.

4. Peel off the mucosa and soft tissue from the mandible. Submit sections of the tumor with mucosa first. Also, submit areas of leukoplakia or any other abnormalities identified.

5. Submit bone margins en face after decalcification. If the tumor is grossly abutting the bone margin, it can also be submitted perpendicularly. If mandibulectomy is performed for sarcoma, the surgeon may request evaluation of bone margins intraoperatively. The bone edges can be scraped off/curetted and submitted for intraoperative evaluation.

6. Submit perpendicular sections of the mandible with areas suspicious for bone invasion or closest to the tumor. For sarcoma specimen, tumor mapping can be performed, especially for postneoadjuvant therapy specimen to assess the tumor viability.

IV. Gross description

Glossectomy

Right partial glossectomy: a partial glossectomy (7.0 x 5.0 x 0.7 cm). On the mucosal surface there is an ulcerated ragged area (2.5 x 1.2 cm). This area is 1.0 cm from the right mucosal edge and more than 1.0 cm from the remainder of the circumferential tissue edges. Cross-sections from anterior to posterior reveal a tan ill-defined tumor measuring 2.5 x 2.0 x 1.8 cm. The closest deep margin is 0.6 cm away. Mucosal and deep margins are submitted for frozen section diagnosis.

Section code

A1: Right mucosal margin, en face

A2: Left mucosal margin, en face

A3: Deep margin, perpendicular

A4-A12: Remainder of the specimen with tumor entirely submitted from anterior to posterior

Mandibulectomy

Right mandible, segmental mandibulectomy: a 12 x 4 x 2 cm segmental mandibulectomy specimen with seven attached teeth. On both sides, buccal and lingual, the cortical plates appear expanded with a bulging mass. The alveolar gingiva is ulcerated and overlays a tumor (2.0 x 1.5 x 1.0 cm). The circumferential mucosal margins are grossly uninvolved (the closest mucosal margin is more than 1.0 cm from the tumor); there is attached unremarkable skeletal muscle. The soft tissue is peeled off the bone to reveal that there is a mandibular bone invasion, through and through. Representative sections submitted. The mandible is sent to the bone laboratory for further processing.

Section code

A1: Buccal mucosa, en face

A2: Lingual mucosa, en face

A3-A8: Entire remainder of mucosa with tumor from anterior to posterior

A9: Possible sublingual glands and lymph nodes

Ink code

Left bone margin: black

Right bone margin: blue

Bone laboratory

A10: Left bone margin en face, ink side down

A11: Right bone margin en face, ink side down

A12-A13: Sections perpendicular through the areas with possible bone involvement

V. Common pathologic findings in head and neck specimens

As previously mentioned, although squamous cell carcinoma is the most common pathologic finding in oral cavity resection specimens, many other types of tumors can also be seen, as well as secondary tumors directly extending or metastasizing to head and neck structures. It is worth mentioning that differential diagnosis of a cystic lesion can be broad, including benign odontogenic cyst/keratocyst, cystic ameloblastoma, mucoepidermoid carcinoma, cystic squamous cell carcinoma, or cystic papillary thyroid carcinoma metastases

in the lymph node. A denuded cyst lesion often precludes a definite diagnosis and should never be called benign. Therefore, it is important to handle all the cystic lesions carefully to preserve the cystic lining.

In addition, the tumor site or epicenter of the tumor are clues to correct diagnosis. For example, a tumor arising from the inferior alveolar nerve in a mandibulectomy specimen may turn out to be a malignant peripheral nerve sheath tumor. Moreover, the relationship of the tumor to an either viable or nonviable tooth may lead to the diagnosis of an odontogenic tumor. The details of pathologic findings in each type of tumor is beyond this chapter, and the reader should refer to a head and neck pathology textbook.

VI. Common potential staging pitfalls and solutions

1. Single or multiple tumors in the specimen

There may be more than one primary tumor in a head and neck resection specimen. It is important to be familiar with the clinical history and imaging findings and review the gross specimens carefully in order not to miss any tumor. Each primary tumor should be described and staged separately.

2. Bone erosion versus bone invasion

Oral cavity tumors are staged pT4a when the tumor invades through cortical bone of the mandible or maxilla. Surface bone erosion doesn’t change tumor staging and shouldn’t be mistaken for true bone invasion.

3. Depth of invasion versus tumor thickness

In the American Joint Committee on Cancer (AJCC) staging manual (8th ed),[1] depth of invasion is included in tumor staging of oral cavity non–HPV-associated squamous cell carcinoma. Depth of invasion should be measured from the basement membrane of adjacent normal mucosa to the deepest point of tumor invasion. It shouldn’t be mistaken for the thickness of tumor. Depth of invasion may be less than tumor thickness in an exophytic tumor and more than tumor thickness in an ulcerated tumor.

4. Per *AJCC Cancer Staging Manual* (8th ed),[1] HPV-related and HPV-unrelated oropharyngeal squamous cell carcinomas are staged differently. In short, the staging of HPV-related oropharyngeal carcinoma is based on tumor size, whereas the staging of HPV-unrelated oropharyngeal carcinoma is based on both tumor size and depth of invasion. In addition, the size of metastatic focus in lymph node and presence of extranodal extension affects the tumor staging in HPV-unrelated oropharyngeal carcinoma but not in HPV-related oropharyngeal carcinoma.

VII. What to include in the pathology report

Here is an example of the College of American Pathologists (CAP) cancer protocol. Please also refer to the AJCC staging manual (8th ed)[1] and the CAP website (www.cap.org) for more information.

Synoptic report

PHARYNX (OROPHARYNX, HYPOPHARYNX, NASOPHARYNX):
Procedure: Excision
Tumor Site: Oropharynx, base of tongue
Tumor Laterality: Left
Tumor Focality: Unifocal
Tumor Size:
  Greatest dimension (centimeters): 1.8 cm
  Additional dimensions (centimeters): 1.5 x 1.0 cm
Histologic Type: Human papillomavirus (HPV)-mediated (positive) squamous cell carcinoma
Histologic Grade: Not applicable
Margins:
  Uninvolved by invasive tumor
    Distance from closest margin (millimeters): 5 mm
    Specify location of closest margin: Lateral mucosal margin
Lymphovascular Invasion: Not identified
Perineural Invasion: Not identified

Regional Lymph Nodes: No lymph nodes submitted or found
Pathologic Stage Classification (pTNM, AJCC 8th ed): pT1 Nx M(n/a)

Head and neck biomarker reporting template

Head and Neck Squamous Cell Carcinoma (HNSCC)
p16 Expression: Positive (>70% diffuse and strong nuclear and cytoplasmic staining)
HPV-DNA (by in situ hybridization): Not performed
HPV E6/E7 mRNA (by in situ hybridization): Positive (cytoplasmic and/or nuclear signals)
HPV-DNA (by polymerase chain reaction): Not performed
HPV E6/E7 mRNA (by reverse transcriptase polymerase chain reaction): Not performed

Reference

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

37. Major Salivary Glands

Li Liang, MD, PhD; Diana Bell, MD

I. Indication for major salivary gland resection

Major salivary gland resections are performed for both primary salivary tumors (eg, pleomorphic adenoma, Warthin tumor, mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, salivary duct carcinoma) and secondary tumors (eg, squamous cell carcinoma, melanoma).[1]

II. What do we expect to see in major salivary gland resection specimens?

Major salivary glands include the parotid gland, the submandibular gland, and the sublingual gland. The parotid gland is the largest salivary gland. It is located in the preauricular subcutaneous tissue and is divided into superficial and deep lobes by the facial nerve. The submandibular gland is located in deep posterior floor of mouth, within the submandibular triangle, which is formed by the anterior and posterior bellies of the digastric muscle, and the body of mandible. Sublingual gland is located in anterior floor of mouth. Fine-needle aspiration/core biopsy is often performed before the surgery; however, the surgeon may also request intraoperative evaluation if the diagnosis is unclear preoperatively. (See Figure 37-1.)

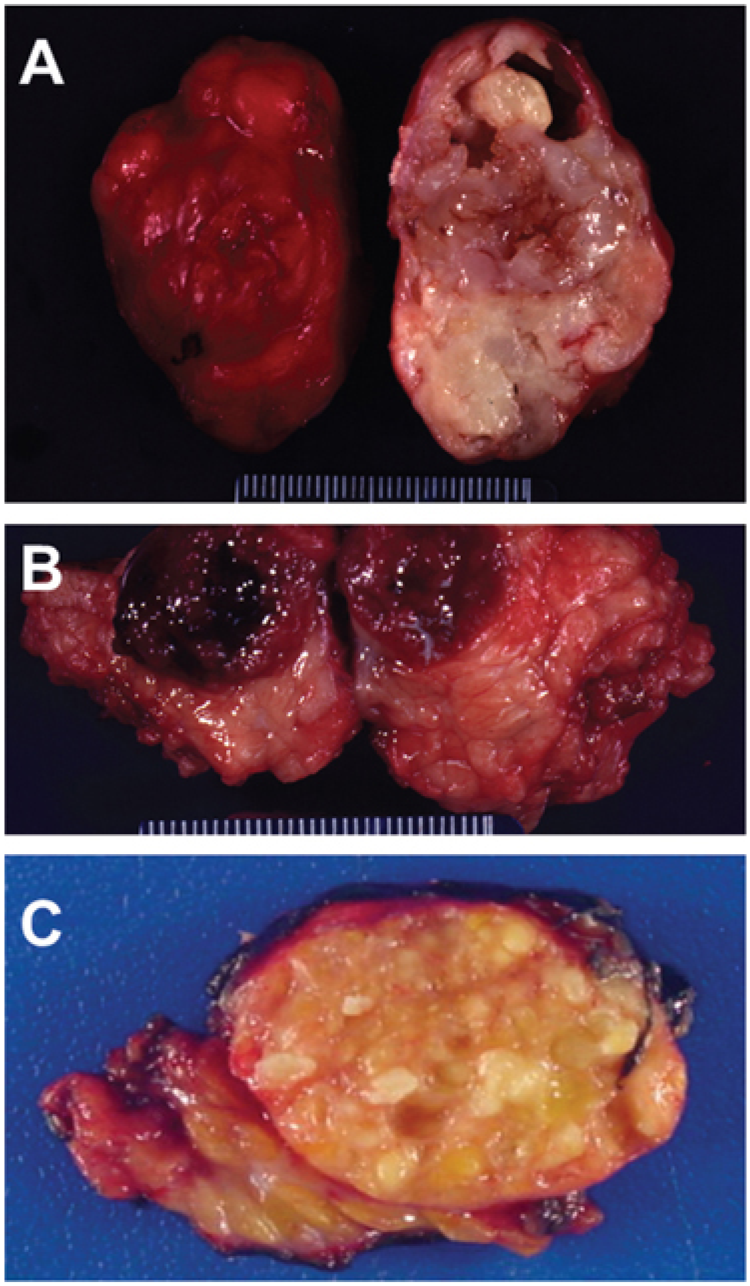

Figure 37-1. Superficial parotidectomy for pleomorphic adenoma (A), Warthin tumor (B), and mucoepidermoid carcinoma (C).

III. Dissection techniques

1. Review the specimen and document the measurements. The deep aspect of a superficial parotidectomy specimen is composed of parotid parenchyma, whereas the superficial aspect is either covered by skin or fascia. It is important to check whether any nerve is present in the specimen.

2. Describe the gross features of the tumor, including color, size, border (ie, encapsulated/circumscribed versus infiltrative), relationship to the nerve and adjacent parotid parenchyma, and whether extraparenchymal extension is grossly identified. Some salivary gland neoplasms have very unique gross features; for example, Warthin tumor has machine-oil–like contents.

3. Measure the distance of the tumor to the closest margin of resection.

4. Submit sections of the tumor with closest resection margins and adjacent parotid parenchyma. It is important to adequately assess tumor borders, especially when carcinoma ex pleomorphic adenoma is in the differential diagnosis.

5. Submit any additional tumor nodules, intraparotid or periparotid lymph nodes, and representative sections of nonneoplastic parotid parenchyma.

IV. Gross description

Right superficial parotidectomy: A superficial lobe of parotid (overall 5 x 4 x 3.8 cm), with a tan-white bosselated mass measuring 3.2 x 2.5 x 2.0 cm. The mass is surrounded by salivary parenchyma and a thin capsule. Representative section of the tumor is submitted for frozen section evaluation. Two possible intraparotid lymph nodes are identified (1.0 cm and 0.8 cm).

Section code

A1: Frozen section, representative section of tumor

A2: Closest peripheral margin (superior)

A3-A10: Remainder of the tumor with deep margin

A11: Two possible intraparotid lymph nodes

V. Common pathologic findings in head and neck specimens

Each salivary gland neoplasm has its unique gross features. For example, pleomorphic adenoma is usually a circumscribed nodule with a tan-white shiny cut surface, which may have pseudopods or satellite nodules. However, any areas of necrosis, hemorrhage, or invasion into surrounding tissue are suggestive of carcinoma ex pleomorphic adenoma. Warthin tumor has typical dark brown, thick, machine-oil–like contents and can be multiple and bilateral. However, sampling of the tumor is still important because mucoepidermoid carcinoma and Warthin tumor can occur in the same patient. In addition, a tumor predominantly involving the subcutaneous tissue in a parotidectomy specimen raises the possibility of a secondary tumor in the parotid gland.

VI. Common potential staging pitfalls and solutions

1. Extraparenchymal extension in major salivary gland neoplasms

Clinical or gross evidence of tumor invasion into soft tissue changes tumor staging of major salivary gland tumors; however, microscopic evidence of extraparenchymal extension doesn't change tumor staging.[2] Therefore, it is important to examine the gross specimen carefully to identify the presence of extraparenchymal/soft tissue extension.

2. Identification of the nerve within the specimen

Sometimes a major salivary gland resection specimen contains a segment of nerve, which may not always be labeled by the surgeon. It is important to examine the specimen carefully and document the presence of any nerve (or tubular structure).

VII. What to include in the pathology report

The following is an example of MD Anderson Cancer Center Diagnostic Template for major salivary gland tumor:

Adenoid cystic carcinoma, tubular and cribriform patterns

Tumor size: 3.0 cm

Extraparenchymal extension: Present

Perineural invasion: Present, multifocal

Lymphovascular invasion: Not identified

Margins of resection: Free of tumor

Here is an example of the College of American Pathologists (CAP) cancer protocol. Please also refer to the American Joint Committee on Cancer staging manual (8th ed)[2] and the CAP website (www.cap.org) for more information.

MAJOR SALIVARY GLANDS:

Procedure: Parotidectomy, total

Tumor Site: Parotid gland, entire

Tumor Laterality: Left
Tumor Focality: Unifocal
Tumor Size:
Greatest dimension (centimeters): 4.2 cm
Additional dimensions (centimeters): 2.5 x 1.0 cm
Histologic Type: Acinic cell carcinoma
High-Grade Transformation: Not identified
Tumor Extension: Extraparenchymal extension clinically and macroscopically identified
Margins:
Uninvolved by carcinoma
Distance from closest margin (millimeters): 5 mm
Specify margin: Deep soft tissue margin
Lymphovascular Invasion: Not identified
Perineural Invasion: Present
Regional Lymph Nodes:
Number of Lymph Nodes Involved: 0
Number of Lymph Nodes Examined: 12
Pathologic Stage Classification (pTNM, AJCC 8th ed): pT3 N0 M(n/a)

References

1. El-Naggar AK, Chan JKC, Grandis JR, et al. *WHO Classification of Head and Neck Tumours.* 4th ed. Geneva, Switzerland: WHO Press; 2017.
2. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

38. Paranasal Sinuses

Li Liang, MD, PhD; Diana Bell, MD

I. Indication for maxillectomy

The most common pathologic finding in maxillectomy specimens is squamous cell carcinoma. However, various tumor types can be seen in head and neck resection specimens, such as odontogenic, salivary gland, and mesenchymal tumors; melanoma; and secondary tumors.

II. What do we expect to see in maxillectomy specimens?

Maxillary sinus, the largest paranasal sinus, is pyramid shaped (see Figure 38-1). The floor of the maxillary sinus is the alveolar process of the maxilla; the roof of the maxillary sinus is formed by the floor of the orbit; the base of the pyramid (medial wall) is the inferior lateral wall of the nasal cavity; the apex of the pyramid points laterally toward the zygomatic bone.

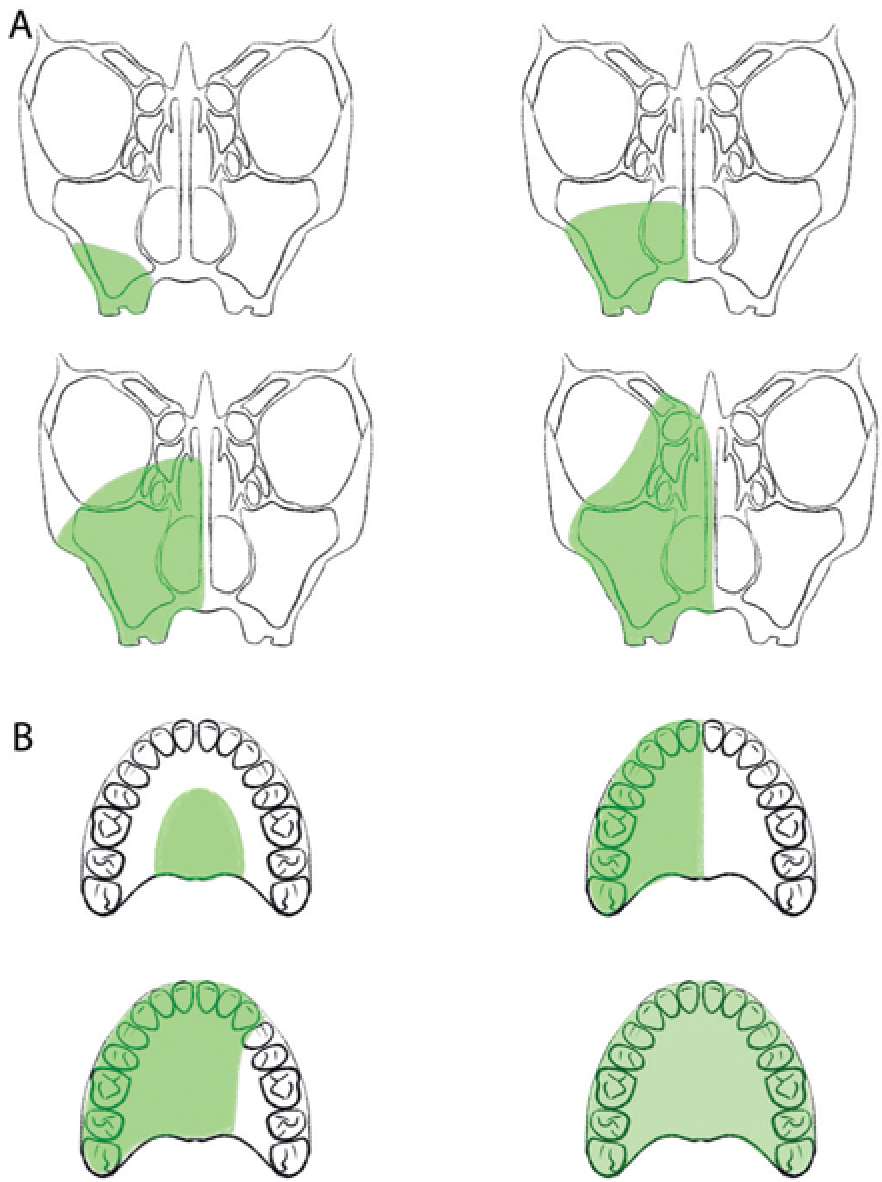

Figure 38-1. Coronal view (A) and oral view (B) of different types of maxillectomy specimens. (Adapted from Brown JS et al.[1])

Infrastructure maxillectomy is most often performed for treating oral cavity tumors. The specimen is composed of the hard palate/roof of mouth and lower portion of the maxilla and teeth, while the orbital floor is preserved (see Figure 38-2.)[1] Total maxillectomy is resection of the entire maxilla with or without orbital exenteration, often performed for treating tumors of the nasal cavity or paranasal sinus (see Figure 38-3).[1]

Figure 38-2. Gross photo of an infrastructure maxillectomy specimen (oral view).

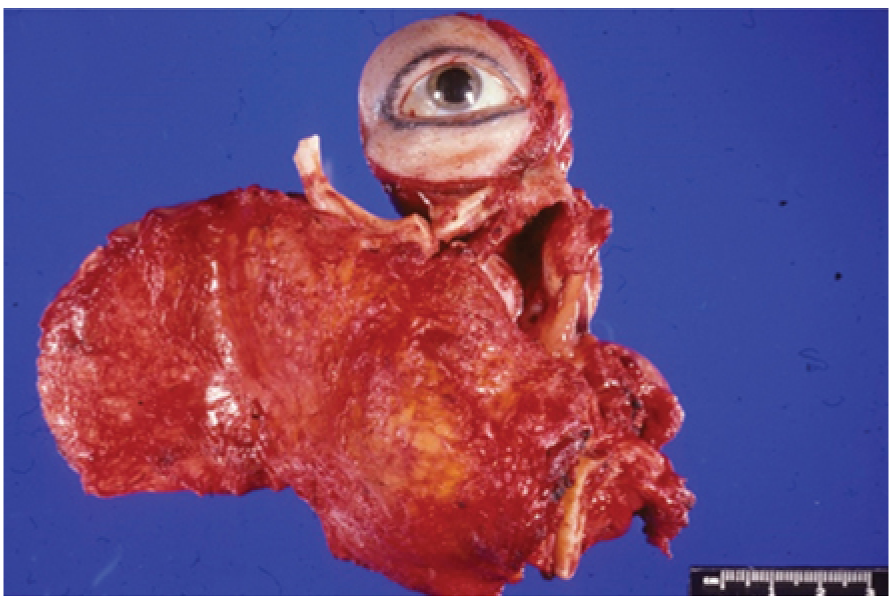

Figure 38-3. Gross photo of a total maxillectomy specimen with orbital exenteration.

III. Dissection techniques: step-by step description

1. Examine the specimen and determine the primary site of the tumor (eg, palate, maxillary gingiva, or maxillary sinus). Correlation with clinical and radiologic findings is recommended.

2. Describe the gross features of the tumor. Document whether the tumor invades the maxillary bone and which part of the bone is involved by tumor.

3. Infrastructure maxillectomy: Peel off the mucosa. Submit the mucosal margins if no separate margins have already been submitted by the surgeon. If the specimen is small, the entire mucosa and soft tissue component can be submitted sequentially. The most important margin for an infrastructure maxillectomy specimen is the anterior margin, which is usually submitted en face unless the tumor is grossly abutting the anterior bone margin.[1] Discuss with the surgeon about the resection margins for an unusual situation (eg, the

specimen is fractured or the patient has multiple previous surgeries). Submit representative sections of the bone with areas suspicious for bone invasion or closest to the tumor.

4. Total maxillectomy without orbital exenteration: Examine whether the specimen contains the roof (floor of orbit); floor (alveolar process); medial (lateral inferior nasal wall), lateral, anterior, and posterior aspect(s) of the maxillary sinus; and whether these structures are grossly involved by tumor. Sample the tumor with adjacent structures adequately.

5. Total maxillectomy with orbital exenteration: In addition to the steps described above, examine whether the tumor invades through the floor of orbit and involves the orbital contents. Submit the margin of optic nerve. If the eye globe is not grossly involved by tumor, it may be examined grossly, or one section with the pupil and optic nerve should be sufficient.

IV. Gross description

Infrastructure maxillectomy

Right maxilla: An infrastructure maxillectomy, including portion of maxilla with one tooth and attached alveolar ridge (overall 3 x 3 x 2.5 cm). Within the gingiva, there is an ulcerated friable mass (2 x 2 x 1 cm), grossly invading the bone. The tumor is rimmed by grossly unremarkable mucosa (the closest mucosa margin is more than 0.5 cm from the tumor); soft tissue is peeled off and entirely submitted in A1 through A6. Bone sent to the bone laboratory for further processing.

Section code

A1-A2: Mucosal rimming

A3-A5: Tumor with adjacent soft tissue

A6: Tumor scooped from alveolar socket

Bone laboratory: The anterior bone margin is submitted en face in A7; sections perpendicular through the areas with possible bone involvement are submitted in A7 through A10.

Total maxillectomy without orbital exenteration

Total maxillectomy: A right total maxillectomy with two teeth (overall dimension 6.5 x 4 x 2.5 cm). The medial aspect of the maxillary bone is missing with visualization of the maxillary sinus. The maxillary sinus mucosa shows a black, slightly elevated and nearly circumferential lesion, measuring 5 x 2 cm. Tumor appears to involve the bone at the anterior portion of the maxilla. The gingival mucosal surface is remarkable.

Section code

A1-A2: Anterior wall of maxillary sinus

A3: Roof of maxillary sinus

A4: Posterior wall of maxillary sinus

A5: Floor of maxillary sinus

A6: Lateral wall of maxillary sinus

A7: Representative sections of gingival and palate mucosa

A8: Bone margin en face

A9-A10: Representative sections of pigmented lesion involving bone (A8-A10 are submitted for decalcification). (Note: The final diagnosis of this case is mucosal melanoma.)

Total maxillectomy with orbital exenteration

Total maxillectomy, left orbital exenteration: A composition resection (overall 13 x 10 x 4 cm), including hard palate (8.5 x 5 x 4 cm, nine teeth), orbital contents with eyelids sparing and globe (9 x 7 x 4 cm). Cross-sections reveal that both the hard palate and orbital contents are extensively involved by a multifocal tumor that entirely destroys the maxilla. There are two distinct tumor nodules, the first centered in the hard palate (4.5 x 4 x 4 cm) and the second nodule within the masticator space and orbit (4 x 4 x 3 cm). The hard palate mucosal edge appears grossly uninvolved. The second dominant nodule within the soft tissue appears to be confined by a pseudocapsule. The tumor extends and involves the orbital soft tissue and possibly the lacrimal gland; however, the skin edges of the eyelids as well as the eye globe are uninvolved. Within the hard palate, the tumor is extending to the anteromedial bone edge. Representative sections submitted.

Section code

A1: Optic nerve margin

A2: Hard palate mucosal edge

A3: Skin edge

A4-A11: First nodule centered in the hard palate

A12-A19: Second nodule from the orbit

A20: Bone margin. (Note: Left infraorbital nerve proximal margin was submitted separately by the surgeon in this case. The final diagnosis is adenoid cystic carcinoma, solid type.)

V. Common potential staging pitfalls and solutions

1. Bone erosion versus bone invasion

Oral cavity tumors are staged pT4a when the tumor invades through the cortical bone of the maxilla. Surface bone erosion doesn't change tumor staging and shouldn't be mistaken for true bone invasion.

2. Handling of specimens with multiple parts

It is not uncommon for the surgeon to submit multiple parts for a head and neck resection; for example, a case of olfactory neuroblastoma may have more than 30 parts. To understand the relationship of different parts, the pathologist not only needs anatomy knowledge, but also effective communication with the surgeon. Although the surgeon usually sends the specimens in sequence with the true margin in the last part submitted, this shouldn't be taken for granted.

3. In an infrastructure maxillectomy specimen, the tumor often originates from the oral cavity and therefore should be staged as an oral cavity carcinoma (see previous chapter).

VI. What to include in the pathology report

Here is an example of the College of American Pathologists (CAP) cancer protocol. Please also refer to the American Joint Committee on cancer staging manual (8th ed)[2] and the CAP website (www.cap.org) for more information.

NASAL CAVITY AND PARANASAL SINUSES:

Procedure: Radical maxillectomy

Tumor Site: Maxillary sinus

Tumor Laterality: Left

Tumor Focality: Unifocal

Tumor Size:

- Greatest dimension (centimeters): 4.0 cm
- Additional dimensions (centimeters): 2.5 x 2.5 cm

Histologic Type: Squamous cell carcinoma, keratinizing

Histologic Grade: G3: Poorly differentiated

Tumor Extension: Tumor invades anterior orbital contents and skin of cheek

Margins:

- Uninvolved by invasive tumor
  - Distance from closest margin (millimeters): 10 mm
  - Specify margin: Medial mucosal margin
- Uninvolved by high grade dysplasia/in situ disease
  - Distance from closest margin (millimeters): 5 mm
  - Specify margin: Medial mucosal margin

Lymphovascular Invasion: Not identified

Perineural Invasion: Present

Regional Lymph Nodes:

- Number of Lymph Nodes Involved: 0
- Number of Lymph Nodes Examined: 12

Pathologic Stage Classification (pTNM, AJCC 8th ed): pT4a N0 M(n/a)

References

1. Brown JS, Rogers SN, McNally DN, et al. A modified classification for maxillectomy defect. *Head Neck.* 2000;22(1):17-26.
2. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

39. Ear

Li Liang, MD, PhD; Diana Bell, MD

I. Indication for auriculectomy

Auriculectomy is performed for tumors of the external ear, most commonly squamous cell carcinoma.

II. What do we expect to see in ear specimens?

Ear specimen includes total auriculectomy and partial auriculectomy.[1] The specimen may include skin, cartilage, underlying temporal bone surrounding the external ear canal, and parotid gland.

III. Dissection techniques

The ear lobe is usually bread-loafed, and the resection margins and representative sections of the tumor are submitted sequentially. It is important to document the maximum depth of invasion and whether the tumor grossly invades the soft tissue and cartilage. The auriculectomy specimen may also contain the parotid gland and a portion of the temporal bone. The relationship of the tumor to the external auditory canal and whether the tumor grossly involves the bone should be documented. The soft tissue adjacent to where the external auditory canal enters the superficial aspect of the temporal bone can be shaved off and submitted en face. The cone-shaped temporal bone should be radially sectioned and entirely submitted after decalcification to assess the entire circumferential bone margins.

IV. Gross description

Total auriculectomy: A total auriculectomy specimen (8 x 7 x 5 cm), consisting of the entire external ear (7 x 2 x 3.5 cm) with adjacent skin, soft tissue, and a cone-shaped temporal bone (2.5 x 1.0 x 1.0 cm) that surrounds the external ear canal. There is a large tan-brown ulcerated lesion (3.0 x 2.5 cm) surrounding the opening of the external ear canal and involving both the tragus and antitragus. The lesion is located 1.0 cm away from the medial skin and soft tissue resection margin, 2.0 cm away from the superior skin and soft tissue resection margin, and 2.0 cm away from the inferior skin and soft tissue resection margin. The tumor grossly invades to a depth of 1.0 cm and invades the underlying cartilage. No definite bone invasion is grossly identified. The tumor is 1.5 cm away from the closest temporal bone margin (inked black).

Section code

A1: Superior skin and soft tissue margin, en face

A2: Inferior skin and soft tissue margin, en face

A3: Medial skin and soft tissue margin, en face

A4-A7: Representative sections of tumor with underlying cartilage and deep soft tissue margin

A8: Shaved soft tissue adjacent to where the external auditory canal enters the superficial aspect of the temporal bone, en face

A9-A11: Circumferential temporal bone margin, radially sectioned and submitted after decalcification

V. Common potential staging pitfall and solution

If the auriculectomy specimen includes a portion of the temporal bone, it is important to submit the entire circumferential bone margin.

VI. What to include in the pathology report

Please refer to the previous chapters of the Head and Neck section.

Reference

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

40. Neck Lymph Nodes

Li Liang, MD, PhD; Diana Bell, MD

I. Indication for neck dissection

Lymph nodes in the neck are removed in patients with a head and neck cancer because there is a high risk that the cancer may have spread to the lymph nodes in the neck, or if it has already spread to those nodes. There are several types of neck dissection, depending on where the cancer is, whether it has spread to the lymph nodes, and whether it has spread to other structures in the neck.

II. What do we expect to see in the neck lymph node dissection?

There are several types of neck dissection: radical, modified radical, and selective neck dissection. Internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve can be present in radical neck dissection specimens and absent in selective neck dissection specimens. In addition, the neck dissection specimen may also contain the submandibular gland and the tail of the parotid gland (see Figure 40-1).

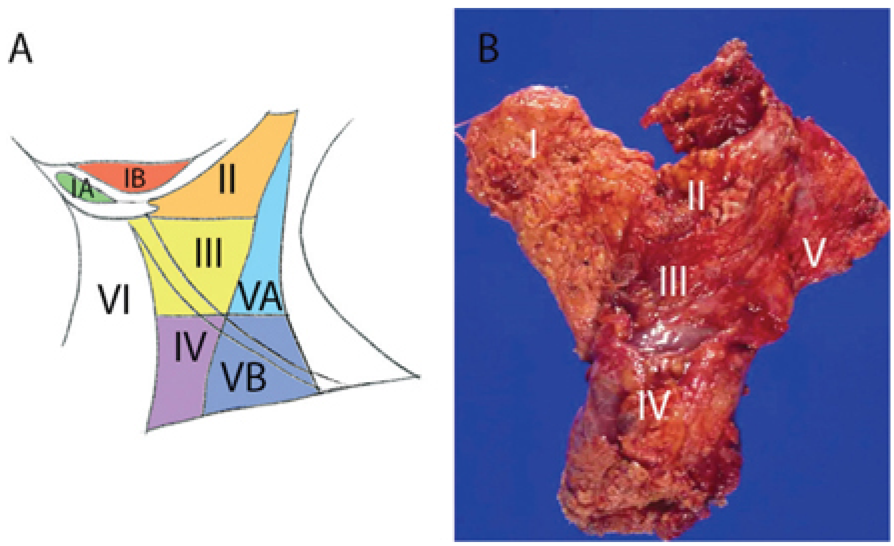

Figure 40-1. Neck lymph nodes. A. Diagram showing the different levels of lymph nodes. B. Gross photos of a neck dissection specimen with the different levels of lymph nodes marked.

IV. Dissection techniques: step-by-step description

1. Orient the specimen and identify the anatomic structures.[1,2]

2. Remove the sternocleidomastoid muscle and open the internal jugular vein along its long axis. (This only applies to radical neck dissection specimens.)

3. Divide the lymph nodes into groups: level IA, submental group; level IB, submandibular group; levels IIA and IIB, upper jugular group; level III, midjugular group; level IV, lower jugular group; levels VA and VB, posterior triangle group.[1]

4. Submit all the lymph nodes with adjacent soft tissue to assess extranodal extension. The lymph nodes should be submitted entirely, except that a large, grossly positive lymph node may be sampled representatively (for example, one section per centimeter). Of note, the assessment of extranodal extension is important especially in non–human papillomavirus (HPV)-associated squamous cell carcinoma.

5. Submit representative sections of submandibular gland, the tail of the parotid gland, and any other anatomic structures present.

V. Common pathologic findings in head and neck specimens

Metastatic squamous cell carcinoma of the neck may derive from the oral cavity, pharynx, skin, and so forth. Immunohistochemical stain for p16 and high-risk HPV testing can be performed for nonkeratinizing squamous cell carcinoma (ie, level II or III lymph nodes). Epstein-Barr virus–encoded RNA (EBER) in situ hybridization can be performed for nonkeratinizing squamous carcinoma or undifferentiated carcinoma suspicious of nasopharyngeal origin. Moreover, squamous cell carcinoma in level V lymph node raises the possibility of metastatic cutaneous squamous cell carcinoma. Metastatic carcinoma from other sites (eg, thyroid, breast, gastrointestinal, and gynecologic cancers) are also seen in neck lymph node dissection. Rarely, two different types of metastatic tumors can be seen in the same resection specimen or even in the same lymph node.

VI. Common potential staging pitfalls and solutions

1. Extranodal extension

Per *AJCC Cancer Staging Manual* (8th ed),[3] minor extranodal extension is defined as tumor extension 2 mm or less from the capsule. Major extranodal extension is defined as grossly identifiable extranodal extension by the pathologist or microscopically extension >2 mm from the lymph node capsule. Tumor deposit in soft tissue without nodal architecture is considered to be the equivalent of a positive lymph node with extranodal extension.[3] Extranodal extension should be measured vertically from the lymph node capsule to the farthest point of extranodal extension.

2. Metastatic carcinoma with cystic change

Metastatic carcinoma with cystic changes (eg, cystic squamous cell carcinoma or cystic papillary thyroid carcinoma) sometimes can be missed during grossing and mistaken as a benign cyst (eg, lymphoepithelial cyst or branchial cleft cyst). We should be familiar with this pitfall.

VII. What to include in the pathology report

1. MD Anderson Cancer Center Diagnosis Template

Metastatic squamous cell carcinoma in one of two lymph nodes (1/2)

Largest tumor focus: 2.5 cm

Extranodal extension: Present, >2 mm

2. In *AJCC Cancer Staging Manual* (8th ed), a new chapter has been added about squamous cell carcinoma in neck lymph nodes arising from an unknown primary tumor of the head and neck.[3]

References

1. Slootweg PJ. Complex head and neck specimens and neck dissections: how to handle them. *J Clin Pathol.* 2005;58(3):243-248.
2. Robbins KT, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. Standardizing neck dissection terminology: official report of the Academy's Committee for Head and Neck Surgery and Oncology. *Arch Otolaryngol Head Neck Surg*. 1991;117(6):601-605.
3. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

41. Bone Marrow

Wenbin Xiao, MD, PhD; Ahmet Dogan, MD, PhD

Bone marrow (BM) examination refers to the pathologic analysis of samples obtained by BM aspiration and biopsy (often called a trephine biopsy) and is essential for the diagnosis and management of many disorders of the blood and BM. The BM aspirate and biopsy are complementary, and both are needed to achieve a comprehensive evaluation of the BM. Adequate sampling and proper processing is a prerequisite for an optimal pathologic interpretation. Standardization of BM specimen preparation, processing, and reporting has been proposed. Here we discuss how to prepare adequate samples, how to process them, and what to include in the pathology report.

I. Indications for BM examination

General indications for BM examination include diagnostic purpose, staging for solid tumors (including lymphomas), and monitoring therapeutic effects.

1. Diagnostic purpose

BM examination is indispensible for the diagnosis and classification of hematologic malignancies, particularly myeloid neoplasms and acute lymphoblastic leukemia. Unexplained peripheral blood findings, such as cytosis, cytopenia, increased blasts, and dysplasia, generally require a BM examination. Other diagnostic indications include evaluation of BM failure syndromes, metabolic storage disorders, and fever of unknown origin.

2. Staging for solid tumors (including lymphomas)

BM workup is required for lymphoma staging purpose. Detection of metastatic solid tumors is critical for clinical management such as small blue round cell tumors of childhood (commonly neuroblastoma, retinoblastoma, and Ewing sarcoma).

3. Monitoring therapeutic effects

BM examination is routinely performed after induction chemotherapy for acute leukemia, consolidation chemotherapy, and pre- and post-hematopoietic stem cell transplantation, for follow-up of myelodysplastic syndromes, myeloproliferative neoplasms, and BM failure syndromes, and for restaging after treatment of lymphoma and small blue round cell tumors of childhood. It can also occasionally used for monitoring toxicity of drugs.

II. Contraindications and complications

BM aspiration and biopsy procedure can be safely accomplished, even in patients with comorbid conditions such as coagulopathy or severe thrombocytopenia. The only absolute contraindications to performing a BM biopsy are the presence of severe hemophilia, severe disseminated intravascular coagulopathy, or other related severe bleeding disorders. Thrombocytopenia, regardless of severity, itself is not a contraindication. Factor transfusion might be needed, but platelet transfusion is seldom necessary unless prolonged oozing from the biopsy site uncontrolled by pressure bandage occurs.

The posterior iliac crest is by far the preferred site for both aspirate and biopsy. Complications are rare if the procedure is performed correctly. Injury to internal nerve and vessels virtually never occurs. Bleeding can be controlled by manually applying pressure to the site. Pressure bandage is usually used for patients with thrombocytopenia. Infection is exceedingly rare and is generally preventable if sterile technique is followed. The anterior iliac crest can be alternative site in obese patients. Due to its potential complications, sternal aspirate is seldom performed. Biopsy should never be performed on the sternum.

III. Components of BM specimen

BM aspirate has been primarily utilized for cytologic assessment, obtaining a differential cell count, and providing material for other ancillary tests, such as cytogenetics, molecular studies, microbiologic cultures, immunohistochemistry, and flow cytometry. BM biopsies, on the other hand, allow evaluation of the marrow's overall cellularity, detection of focal lesions, and determination of the extent of infiltration by various pathologic entities. Hence the BM aspirate and biopsy provide complementary information. Doing aspiration or biopsy alone would miss the diagnosis in up to 10% to 30% of the patients, particularly with "focal" processes such as lymphoma, multiple myeloma, and metastatic tumor. Even for acute leukemia and myeloid neoplasms, evaluation of both aspirate and biopsy often provides more comprehensive results. Therefore, it is recommended that both aspiration and biopsy should be routinely performed so that respective findings can be correlated.

For leukemia, myeloid neoplasms and plasma cell neoplasm, unilateral sampling is generally adequate. Although positron emission tomography-computed tomography (PET-CT) scan has been integrated into BM staging of lymphoma with strong negative predictive value, BM sampling is still the gold standard, and an adequate unilateral sampling including a biopsy of 1.6-cm to 2-cm length is necessary. Bilateral sampling is routinely performed for staging small blue round cell tumors of childhood.

A detailed discussion on the techniques used to obtain BM aspirate and biopsy can be readily found elsewhere and is beyond the scope of this chapter.

IV. Processing of BM aspiration

Once BM is aspirated, several preparations can be made. The first nonanticoagulated fluid marrow (approximately 0.5 mL) should be used for morphologic assessment. Basically, individual drops of the marrow are quickly discharged onto upper edges of inclined slides. Particle crush smears (see Figure 41-1A,B) or direct smears (see Figure 41-1C,D) can be prepared. Buffy coat smears are not routinely used in most of the laboratories and thus will not be discussed here. The advantages and disadvantages of different preparations are compared in Table 41-1.

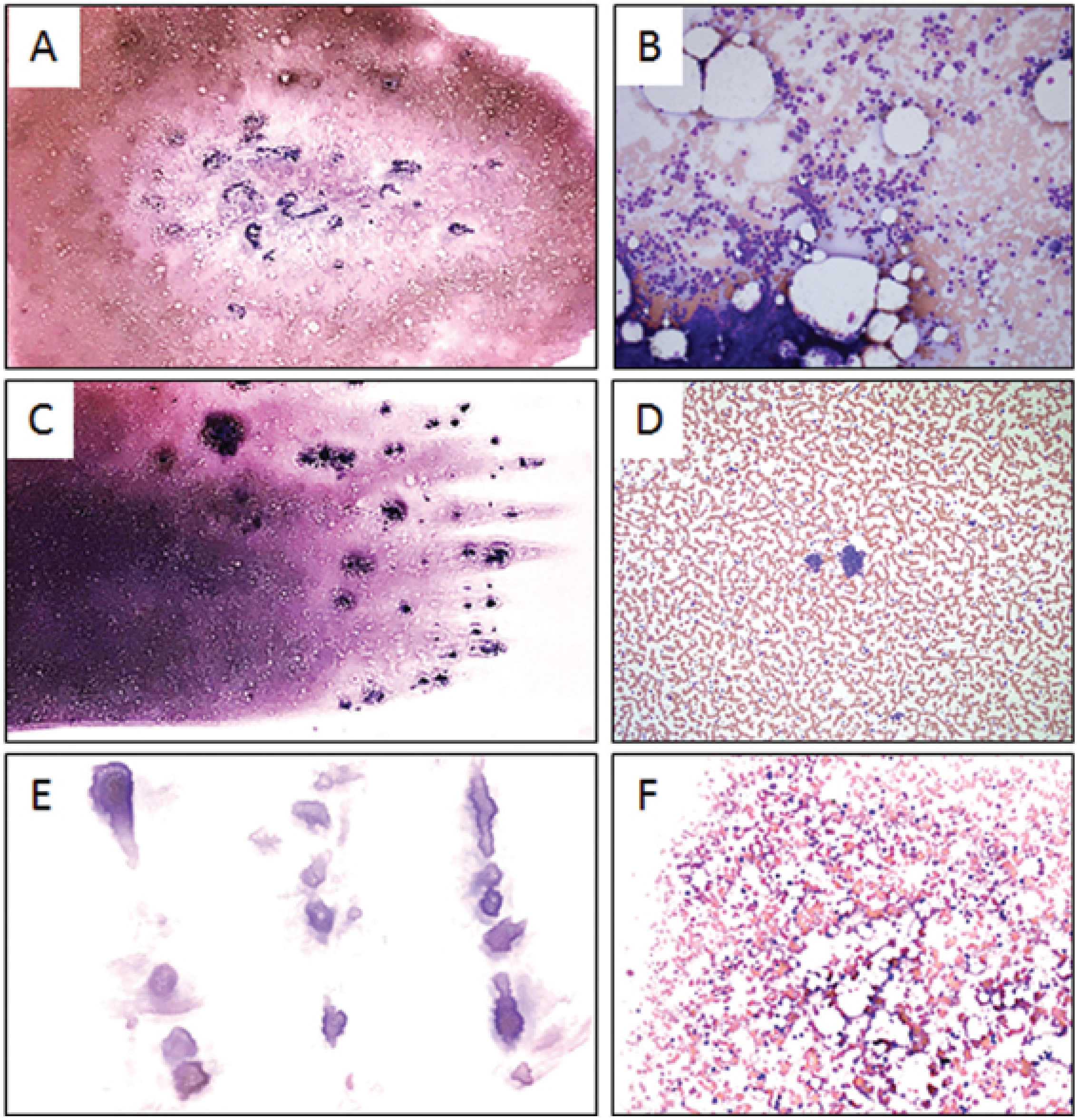

Figure 41-1. Bone marrow smears and clot sections. A, B. Particle crush smear. C, D. Direct smear. E, F. Imprint smear.

Table 41-1. Comparison of Bone Marrow (BM) Preparation

Preparation	Procedure	Advantages	Disadvantages	Stain and method of analysis
Direct smears	Similar to that for a blood smear; place a few particles at one end of a slide and spread with another slide	Excellent morphology Staining uniform Differential counts generally accurate	May be diluted by blood, causing skewed cell counts	Wright-Giemsa Dacie Cytochemistry Immunocytochemistry Prussian blue Sideroblasts stain Can be used for fluorescence in situ hybridization (FISH) and molecular testing
Particle crush smears	Place a few particles on a slide, put another slide on top, and gently compress and pull apart the 2 slides	Useful for evaluation of megakaryocytes, mast cells, macrophages, and cancer cells Best for assessing storage iron	Many cells may be broken and have bare nuclei Cell dispersal and staining very uneven	
Buffy coat smears	Particles are concentrated from anticoagulated aspirate, stirred extensively and mixed with plasma	Even distribution Excellent morphology Staining uniform	Aggregates of normoblasts may skew differential counts Blasts may be underestimated All cell-to-cell interrelationship lost	
Imprint smears	The biopsy is gently and repeatedly touched to the slide or vice versa	Maybe the only way to access cytology and perform differential count if aspirate unsuccessful	Distorted morphology Skewed differential counts	
Clot sections	Remaining particles are clotted and wrapped in tissue paper, processed, and sectioned	Assessment of cellularity and megakaryocyte numbers particularly in the absence of biopsy Not decalcified compatible with molecular testing	Cellularity may be inaccurate Reflects only cell type and lesions that are aspirable	Hematoxylin-eosin (H&E) Periodic acid-Schiff (PAS) Giemsa Immunohistochemistry Prussian blue Sideroblast stain Molecular testing
Biopsy sections	Fixed, decalcified, processed, and sectioned	Best for evaluating focal processes, patter of infiltrate cellularity, interrelationships of cell types, distribution of cells, bone, blood vessels, stromal elements, fibrosis, necrosis	Decalcification destroys some enzymes and antigens May be incompatible with some immunohistochemical and cytochemical stains Incompatible with molecular testing	H&E PAS Giemsa Reticulin Immunohistochemistry When fresh collected and prior to fixation, can also be used for cytogenetics, flow cytometry, molecular testing, and culture in case of a "dry-tap"
Aspirate fluid	Anticoagulated (EDTA)	Flow cytometry, molecular testing, karyotyping, and FISH	—	Flow cytometry Cyrogenetics FISH Molecular testing Culture

Additional aspirate fluid should be obtained and placed in tubes containing anticoagulant and sent for flow cytometry and cytogenetic and molecular testing. These tests can be canceled if considered to be unnecessary after reviewing the BM slides. The types of anticoagulant depend on the test. Although it is suggested that the aspirate for flow cytometry should be collected into a sodium heparin tube, heparin interferes with molecular tests. At the Memorial Sloan Kettering Cancer Center, we routinely use EDTA and analyze the sample within 12 to 24 hours.

The remaining aspirated marrow, after clotting, can be routinely processed and sectioned to provide additional morphologic evaluation, especially when the biopsy is not performed or is not obtainable. The clot sections, different from biopsy, can also be used for molecular testing if necessary.

If aspiration is not successful (for example in patients with marked fibrosis), the biopsy becomes indispensible. Imprint smears can be made by gently touching the BM biopsy to a slide or vice versa (Figure 41-1E,F).

Sample procedure

1. Place 10 clean glass slides on a flat surface and incline at an angle.
2. Discharge the BM aspirate from the syringe onto upper edges of the two inclined slides. Blood will drain to the bottom of the slide leaving the particles near the top and middle.
3. Use the edge of a clean slide to pick up several particles from the aspirate specimen on the inclined slides.
4. Place the slide with spicule in a horizontal position on top of another clean slide approximately 2 cm from the edge.
5. Pull the slides apart longitudinally while maintaining contact between the two slides. This should be done gently without pressure.
6. Repeat for the rest of slides.
7. Allow the slides to dry completely.
8. All slides should be labeled with at least two identifiers.
9. The slides are then placed in labeled coin envelopes/slide boxes/plastic slide containers.
10. The slides are delivered to BM laboratory for staining.

V. Processing of BM biopsy

Adequate BM biopsy sections are ideal for evaluating involvement by focal processes, the pattern of infiltrate, bone trabeculae, and necrosis. In addition, BM cellularity is more accurately estimated based on the BM biopsy (Figure 41-2).

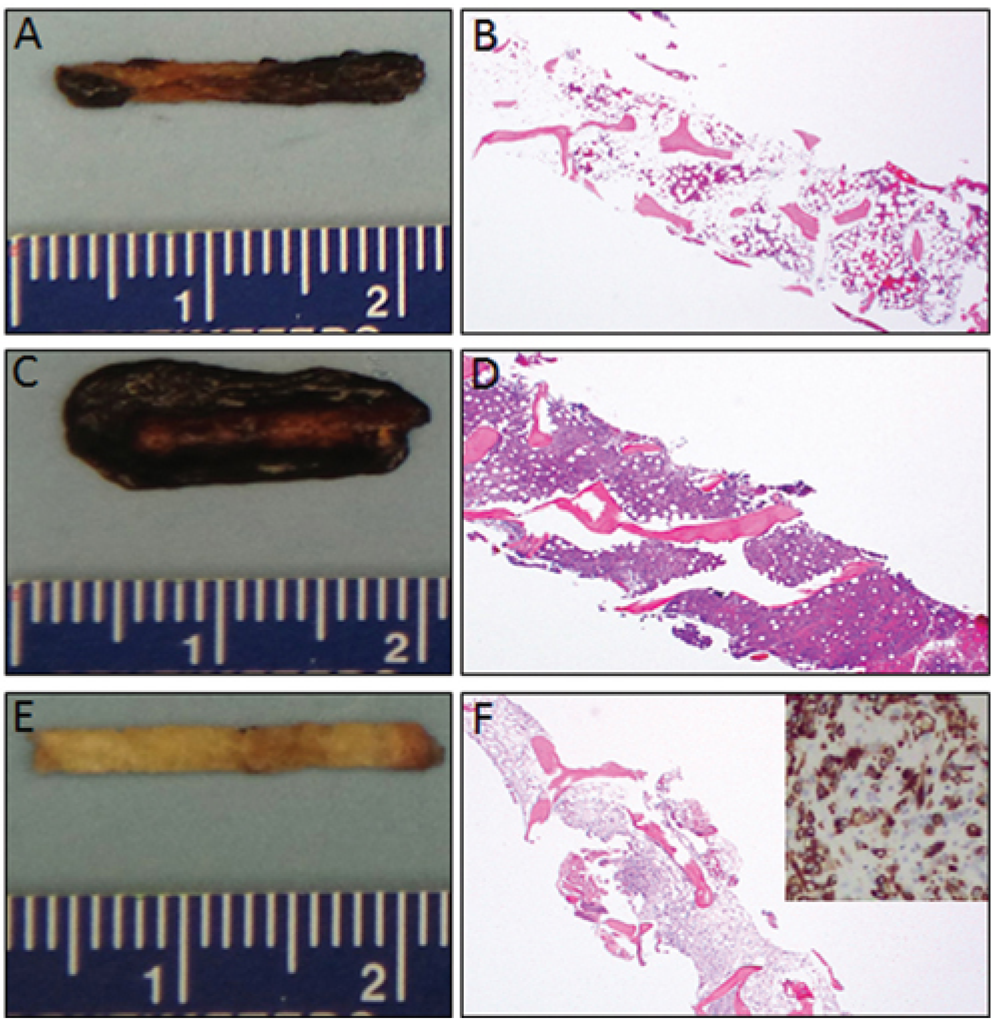

Figure 41-2. Bone marrow (BM) biopsy. A. Gross picture of a postchemotherapy BM biopsy. B. Low-power view of the biopsy. C. Gross picture of a day 60 posttransplant BM biopsy. D. Low-power view of the biopsy. E. Gross picture of a BM biopsy from a leukemia patient. F. Low-power view of the biopsy (insert: CD34 immunohistochemical stain).

Plastic embedding offers unique advantages such as thinner sections and no requirement for decalcification, but it is time consuming and not cost efficient. Therefore, paraffin embedding has been routinely used for BM biopsy in the vast majority of the laboratories. When the biopsy specimen is ready, imprint smears should be quickly made if necessary. In addition, if aspiration is unsuccessful or inadequate for specialized studies (see below), a fresh extra BM biopsy sample can be obtained, and cells can be disaggregated by crushing and then flushing the specimen using RPMI 1640 or normal saline.

The first step to process BM biopsy is fixation. A standard fixative is neutral buffered formalin. The other commonly used fixative buffers include B5 (mercuric chloride, sodium acetate, and formalin), Zenker's, and zinc formalin. The fixation times vary depending on different buffers: neutral buffered formalin, at least 18 to 24 hours; B5, 2 hours; Zenker's fixative, at least 3 to 4 hours; and zinc formalin, 3 to 4 hours. Mercury-based fixatives such as Zenker's and B5 solutions provide excellent cytologic detail, but they may be incompatible with certain immunohistochemical studies. Cost and environmental issues are other factors that have led many laboratories to switch to alternative fixatives. If the BM biopsies are processed along with other surgical specimens, neutral buffered formalin is preferably used. Excellent morphologic detail can be achieved providing adequate fixation time is ensured.

Decalcification is achieved by placing the biopsy in decalcification buffers. Commonly used commercial decal buffers are Decal Stat (1 hour), RDO (40-60 minutes), and Surgipath Decalcifier II (90 minutes). Decalcification with EDTA results in better preservation of nucleic acids but is slower than with other acid reagents. After adequate decalcification, the specimens should be processed in an automatic tissue processor.

Thin sections (2-3 μm in thickness, no more than 4 μm) should be prepared on the BM biopsy and submitted for hematoxylin-eosin staining. Other stains can be performed on the biopsy such as immunohistochemical stains, reticulin stain, periodic acid-Schiff (PAS), and Giemsa. Iron stain is not recommended on biopsy due to high false-negative rate caused by the chelation of iron during decalcification process.

Sample procedural note

1. BM biopsy specimen received in formalin is rinsed in water for 15-30 minutes.
2. Placed in Formica-4 for 1 hour.
3. Washed in water for 10 minutes.
4. Placed in Decal-Stat for 1 hour.
5. Placed in running water for 5 minutes.
6. Decalcified BM biopsy specimen is placed in a cassette and the cassette is placed in Lithium solution for 5 minutes to remove salts.
7. Wash well in running water for 15-30 minutes.
8. Load onto processor for embedding.
9. Blocks are cut at 2-μm thickness and placed on glass slides.

V. Sample preparation for specialized techniques

Specialized studies are critical for diagnosis, prognosis, and disease monitoring. The most commonly utilized special techniques for BM examination are immunohistochemistry, karyotyping, fluorescence in situ hybridization (FISH), flow cytometry, and molecular diagnostics. Immunohistochemistry can be done on biopsy sections, but the antibodies need to be validated as some antigens are destroyed by decalcification. Fresh aspirate is required for karyotyping and flow cytometry studies. As mentioned above, cells disaggregated from the fresh collected core biopsy can also be used in case of inaspirable conditions. FISH can be done on air-dried smears. Decalcification is incompatible with molecular testing; therefore, either fresh samples or formalin-fixed samples are often needed, although cells scraped from smears and/or clot sections can be also used. Cytochemistry is less often utilized largely due to the advancement in flow cytometry immunophenotyping. Iron stain should be performed on smears or clot section.

VI. What to Include in the pathology report

A thorough BM evaluation includes a review of the relevant clinical and laboratory results as well as examination of the peripheral blood smear, BM aspirate smear, and biopsy. The final report should include the diagnosis, the pathologist's recommendation for further studies if necessary, and supporting data.

It is highly recommended to issue a pathology report integrating BM aspirate, biopsy, CBC, peripheral blood smear, flow cytometry, and cytogenetic and molecular results. As the results of cytogentic and molecular studies are often logistically delayed, the report should list the special testing being performed on the aliquots of the specimen.

A BM nucleated cell differential count should be performed. Only nucleated cells are counted including blasts, promyelocytes, myelocytes, metamyelocytes, band/segmented neutrophils, eosinophils, basophils, mast cells, promonocytes, monocytes, lymphocytes, plasma cells, and erythroblasts. Megakaryocytes, macrophages, osteoblasts, osteoclasts, stromal cells, smudged cells/barre nuclei, or nonhematopoietic cells such as metastatic cancer cells are not counted. At least 500 cells should be counted in at least two smears when a precise percentage of an abnormal cell type is required for diagnosis and disease. At least 300 cells should be counted if the differential count is not essential to the diagnosis. The myeloid:erythroid (M:E) ratio should be calculated by expressing the ratio of all granulocytes and monocytes and their precursors to erythroblasts. Differential count may be unnecessary in the setting of metastatic carcinoma.

Sample template of BM report

1-3. Bone marrow, right posterior iliac crest, biopsy; aspirate and peripheral blood smears:

Therapy-related myeloid neoplasm, specifically myelodysplastic syndrome with excess blasts 2 (MDS-EB2, 11% blasts on touch imprint).

COMMENT

The patient's history of breast cancer status post chemoradiation therapy supports the above diagnosis. Correlation with pending cytogenetic and mutational results is suggested for further characterization.

BONE MARROW BIOPSY

Quality: adequate

Cellularity: 50%

M:E ratio: normal

Blasts: increased

Myeloid lineage: adequate and left shifted

Erythroid lineage: present and orderly maturing

Megakaryocytes: adequate with dysplasia (clustering, monolobation and separate nuclear lobation)

Lymphocytes: rare

Plasma cells: rare

Special stains: Reticulin stain shows no increase in reticulin fibrosis (MF-0).

Clot section: similar to biopsy

BONE MARROW ASPIRATE SMEAR

Differential: (Performed by HWH)

Touch imprint

Blasts 11%

Promyelocytes 4%

Myelocytes 10%

Metamyelocytes 6%

Neutrophils/Bands 27%

Monocytes 6%

Eosinophils 1%

Erythroid Precursors 18%

Lymphocytes 17%

Number of Cells Counted 500

M:E Ratio 3
Sideroblast stain:
Iron: adequate
Ring sideroblasts: absent
Morphology:

The aspirate smear is aspicular, paucicellular and hemodiluted, suboptimal for evaluation. The touch imprint is cellular showing mildly increased blasts. The blasts are medium in size and have a rim of blue agranular cytoplasm, round nuclei, pale chromatin and conspicuous nucleoli. Myeloid lineage shows left shifted maturation. Erythroid precursors show mild dysplasia (nuclear irregularity and budding). Megakaryocytes are rare.

PERIPHERAL BLOOD
CBC (xx/xx/2018):
WBC 6.5 [4.0-11.0 K/mcL]
RBC 1.96 L [3.80-5.00 M/mcL]
HGB 8.2 L [11.2-15.4 g/dL]
HCT 24.1 L [34.3-46.0 %]
MCV 123 H [80-98 fL]
MCH 41.8 H [27.0-33.0 pg]
MCHC 34.0 [31.0-36.5 g/dL]
RDW 14.5 [12.2-15.1 %]
Platelets 41 L [160-400 K/mcL]
Neutrophil 65.1 [32.5-74.8 %]
Lymph 21.5 [12.2-47.4 %]
Mono 10.5 [0.0-12.3 %]
Eos 0.8 [0.0-4.9 %]
Baso 0.2 [0.0-1.5 %]
Immature Granulocyte 1.9 H [0.0-0.6 %]
Immature Granulocytes include metamyelocytes, myelocytes and promyelocytes.
Abs Neut 4.2 [1.5-7.5 K/mcL]
Abs Lymph 1.4 [0.9-3.2 K/mcL]
Abs Mono 0.7 [0.0-1.3 K/mcL]
Absolute Eosinophil 0.0 [0.0-0.7 K/mcL]
Absolute Basophil 0.0 [0.0-0.2 K/mcL]
Nucleated RBC 0.0 [%]

Morphology: anemia and thrombocytopenia. Granulocytes show left shift maturation. There is no overt dysplasia. Circulating blasts are not seen.

IMMUNOHISTOCHEMISTRY
CD34 and CD117 show increased blasts, approximately 10%.

FLOW CYTOMETRIC ANALYSIS, BONE MARROW (F18-xxxx)
Abnormal myeloid blast population detected.
No abnormal B and T cell populations detected.

The blasts have abnormal expression of CD15 (minute subset), CD56 (partial), CD13 (bright), CD33 (bright), CD38 (dim), CD45 (dim) and HLA-DR (dim); with normal expression of CD4, CD34, CD71, CD117 and CD123; without CD2, CD5, CD7, CD8, CD10, CD11b, CD14, CD16, CD19, CD20, CD25, CD64 or surface light chains. CD34 positive myeloid blasts represent 0.60% of WBC.

Mostly mature granulocytes and monocytes seen in the sample, suggestive of hemodilution. Sensitivity of analysis for myeloid neoplasm is reduced. Results may not be indicative of bone marrow composition.

FLOW CYTOMETRIC ANALYSIS, PERIPHERAL BLOOD (F18-xxxx)
Abnormal myeloid blast population detected.

No abnormal B and T cell populations detected.

The blasts have abnormal expression of CD56 (partial), CD13 (bright), CD33 (bright), CD34 (dim), CD38 (dim), CD45 (dim), CD71 (dim), CD123 (bright) and HLA-DR (dim); with normal expression of CD4 and CD117; without CD2, CD3, CD5, CD7, CD8, CD10, CD11b, CD14, CD15, CD16, CD19, CD20, CD25, CD64 or surface light chains. CD34 positive myeloid blasts represent 0.92% of WBC.

CYTOGENETIC STUDIES

Cytogenetic analysis will be reported separately. See separate report, CG18-xxxx.

MOLECULAR STUDIES

Molecular analysis will be reported separately. See separate report, M18-xxxxx to M18-xxxxx

42. Lymph Node, Extranodal Tissue, and Spleen

Wenbin Xiao, MD, PhD; Ahmet Dogan, MD, PhD

The accurate diagnosis and proper management of a patient with lymphoid neoplasms rely on the availability of adequate diagnostic tissue. Morphologic assessment is the key to generate a range of differential diagnosis. Ancillary tests are often necessary to render a precise diagnosis and to provide relevant information on guiding the management. It is imperative for the pathologist to ensure the optimal procurement and processing of lymph node specimens. This chapter reviews the essential steps for producing high-quality histologic sections of lymph node specimens and procuring tissue for ancillary tests. Extranodal tissue and spleen specimens will also be briefly discussed.

I. Types of nodal specimens

The biopsy should be obtained from the most abnormal lymph node, usually the one with largest size and/or with highest fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scan (if available). The type of biopsy is dependent on the accessibility of the node and the complexity of the potential diagnosis. Excisional biopsy of the entire abnormal lymph node is the preferred specimen for the diagnostic purpose. However, minimal invasive procedures, such as fine-needle aspiration (FNA) and core biopsy, even though they often pose diagnostic challenges, are usually more appealing to both the patients and clinicians. FNA specimens are submitted to the cytology service and will not be discussed here.

Excisional biopsy

Excisional biopsy provides more representative tissue for diagnostic workup and subsequent ancillary tests. Simple excision with localized anesthesia can be performed on superficial nodes. However, sometimes laparoscopic and mediastinoscopic approaches may be necessary to access the most abnormal but deeply seated nodes under generalized anesthesia.

Needle core biopsy

Needle core biopsy is less invasive. Computed tomography (CT)-guided core biopsy is extremely useful for deeply localized nodes. The biggest disadvantage is the limited amount of tissue that can be obtained. Not infrequently, a repeat biopsy might be needed due to insufficient tissue for a definitive diagnosis.

II. Processing of nodal biopsy

1. Gross examination

Lymph node biopsy, once taken out, should be placed into a container filled with a balanced physiologic solution (ie, RPMI 1640 or normal saline) to prevent dry-out artifacts. The specimen should be transferred to the laboratory within 1 hour if transported at ambient temperature or within 12 to 24 hours if transported at 4°C. If these specimen transport conditions cannot be met, it is recommended that the specimen should be immediately placed in a fixative (see below). Upon arrival in the laboratory, the specimen should be grossed quickly to avoid autolysis and help with fixation. The gross appearance of lymph nodes, including their size, color, consistency, and changes in structure, should be documented. Preservation of the hilus suggests a reactive process. Lymphomas usually present as a complete effacement of the nodal architecture (Figure 42-1). Necrosis can be seen in both neoplastic and reactive particularly infectious process, but its presence may prompt microbiologic culture studies.

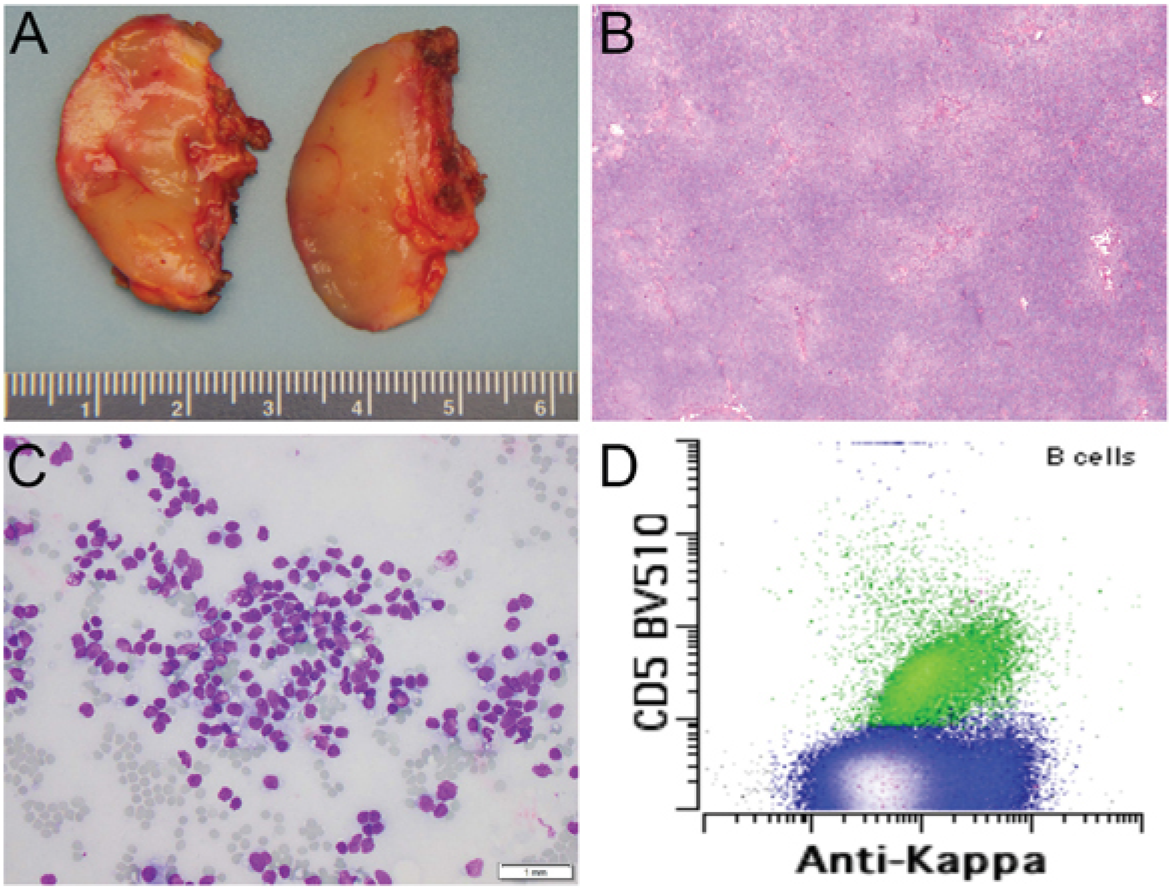

Figure 42-1. A. Gross picture of an excised supraclavicular node. B. Low-power view of the histologic section showing vaguely nodular pattern. C. Touch imprints showing monotonous lymphoid population with occasional plasmacytoid cells. D. Flow cytometric analysis demonstrated two kappa light chain restricted B-cell populations: one CD5 positive and the other CD5 negative. Single nucleotide polymorphism (SNP) array studies were performed on flow sorted cells and revealed *MALT1* deletion in both populations, suggestive of clonal relatedness.

2. Frozen sections and touch imprints

Frozen section is informative for nonhematolymphoid processes such as metastatic carcinoma. If a diagnosis of lymphoma is suspected, frozen sections are strongly discouraged in practice due to the numerous artifacts introduced by the frozen process. If a rapid interpretation is needed, for example, to evaluate the adequacy of the biopsy, touch imprints can be done after sectioning the nodes. If frozen section cannot be avoided, the pathologist should instruct the surgeon to obtain adequate fresh tissue for permanent sections and ancillary tests.

3. Sectioning

Excisional lymph node biopsies should be thoroughly and thinly sliced in order to prevent sampling errors and to allow adequate penetration by fixative buffers. Unsectioned whole nodes are likely not to be well fixed and can have central autolysis.

A single cut along the long axis is recommended for small nodes. Larger nodes are sliced entirely into 2- to 3-mm thick slices. The number of submitted slices varies depending on the clinical settings. In general, three representative slices are adequate for a lymphoma diagnosis. It is recommended that, if the lymph node biopsy is larger than 5 mm diameter, a piece of the fresh lymph node specimen is submitted for ancillary testing. The remainder of the tissue should be retained in fixative buffers in case a go-back is needed.

4. Fixation

After touch imprints are made and fresh tissue is procured for ancillary tests (for example, flow cytometry), the slices should be fixed immediately. Lymph nodes should never be left unfixed. Adequate fixation is of paramount importance in achieving excellent morphology. Poor fixation cannot be reversed and is often the leading cause of uninterpretable nodal biopsies.

The commonly used fixatives include neutral buffered formalin and metal-based fixatives such as B5, neutral Zenker's solution, and zinc formalin. Most laboratories use 10% neutral buffered formalin as it offers the best overall results by providing excellent morphologic preparations, good preservation of immunoreactivity, compatibility for molecular diagnostic tests, and long-term storage of fixed tissue. Ideally, each slice should be placed into a separate block. This allows multiple sections to be cut for immunohistochemistry and genetic studies, preventing premature depletion of the tissue. The time required for fixation in 10% neutral buffered formalin is at least 12 hours but should not exceed 24 hours. Metal-based fixatives can provide excellent nuclear details; however, they are unsuitable for molecular diagnostic tests, require special chemical hazard handling, and are unstable for long-term storage.

III. Sample types suitable for ancillary studies

Fresh tissue is required for microbiologic cultures, flow cytometry, and karyotyping. Other tests, such as immunohistochemistry, in situ hybridization, fluorescence in situ hybridization (FISH), and molecular tests can be performed on many types of tissue (see Table 42-1). Increasingly, most clinically relevant genetic alterations can be assessed in formalin-fixed paraffin-embedded specimens, and fresh specimens for karyotype or molecular analysis are deemed essential. Ancillary studies can be extremely helpful in complicated cases (see Figure 42-1).

Table 42-1. The Suitability of Tissue Types for Ancillary Studies

Studies	Fresh tissue	Frozen tissue	Formalin-fixed, paraffin-embedded tissue	Imprints/cytospin
Microbiologic cultures	Yes	No	No	No
Flow cytometry	Yes	No	No	No
Karyotyping	Yes	No	No	No
Immunohistochemistry	Yes	Yes	Yes	Yes
In situ hybridization	Yes	Yes	Yes	Yes
Fluorescence in situ hybridization	Yes	Yes	Yes	Yes
Molecular diagnostic tests	Yes	Yes	Yes	Yes

IV. Extranodal tissue and spleen

The principle of processing extranodal tissue is similar to that of the nodes. Splenectomy, once a common diagnostic, staging, and treatment modality of hematological neoplasm, is only infrequently performed. It is critical to know the clinical history before grossing. The specimen needs to be carefully examined; for example, a rupture of capsule should be documented in a patient with splenectomy due to trauma. Any perisplenic nodes should be dissected and submitted for evaluation. The spleen is then thinly sliced. Any nodules or localized lesions should be documented. Representative sections of the normal and abnormal spleen parenchyma (usually 2-3 blocks) and splenic hilar lymph nodes should be submitted for routine tissue processing. If a hematologic malignancy is suspected, three to four sections are usually adequate, and the specimen should be handled in a way similar to that for nodal biopsy. Fresh tissue should be procured for flow cytometry and karyotyping. If storage disease is suspected, tissue should also be reserved and fixed in glutaraldehyde for possible electronic microscopy.

V. What to Include in the pathology report

As ancillary tests are generally necessary for the diagnosis of lymphoid malignancies, it is highly recommended to integrate this information into the pathology report. Some tests may not be available for weeks, such as cytogenetic and molecular diagnostic studies. In this case, the report should at least list the ancillary tests being performed on the aliquots of the specimen. An addendum can be followed once the results are available.

Example pathology report

1. Midline mesenteric mass, needle core biopsy:

Follicular lymphoma, grade 1-2, nodular pattern

MORPHOLOGY

The core biopsy shows lymphoid tissue with vaguely nodular pattern. The nodules lack polarization and tangible body macrophages. The nodules are predominantly composed of centrocytes with irregular cleaved nuclei and inconspicuous nucleoli. The centroblasts are larger with dispersed chromatin and irregular nuclei, and prominent nucleoli. The nodules display less than 15 centroblasts/ HPF. A diffuse large cell component is not seen.

IMMUNOHISTOCHEMISTRY

The neoplastic cells

Express: CD20, PAX5, BCL2, BCL6, CD10, and LMO2

Do not express: CD3, MUM1, CD23, CD21

Other:

CD23 and CD21 highlight follicular dendritic meshworks.

Ki67 proliferation index is ~ 10% in the nodular areas.

FLOW CYTOMETRIC ANALYSIS (F18-8xxx)

Abnormal B-cell population identified.

No abnormal mature T-cell population detected.

Flow cytometry reveals an abnormal mature B-cell population having abnormal expression of CD10, CD19 (dim), CD20 (bright), CD22 (bright), CD38 (dim) and lambda light chain restriction; with normal expression of CD45 and without significant CD5. The abnormal B-cell population accounts for 28.8% of the total white cells.

CYTOGENETIC STUDIES (CG18-xxx)

See separate report (pending).

MOLECULAR STUDIES (M18-xxxx)

See separate report (pending).

43. Ophthalmic Enucleation

Patricia Chévez-Barrios, MD

Intraocular tumors are seldom biopsied before radical treatment: radiation, chemotherapy, or enucleation. Transparency of media and integrity of the retina are essential in maintaining visual acuity. Intraocular biopsies may have complications that could alter this integrity, including vitreous hemorrhage or retinal detachment. Retinoblastoma is the most common primary malignant intraocular tumor in children and the most common primary malignant intraocular tumor worldwide. Retinoblastoma tumors can be cured in more than 95% of patients when they are contained to the intraocular structures, but when there is extraocular extension there is more than 80% chance of recurrence. Thus, any tumor seeding into the extraocular tissues during a fine-needle aspiration biopsy would place the patient at risk for metastasis. Uveal melanoma represents the most common malignant intraocular tumor in adults and it is usually treated by brachy radiotherapy if the tumor is less than 15 mm in maximum diameter. If the tumor is larger or has retinal detachment or neovascular glaucoma or has extraocular extension it is usually enucleated. Sometimes uveal melanomas are biopsied prior to placement of the radiation plaque. The biopsies, however, may be complicated by hemorrhage, retinal detachment, or extraocular extension of tumor. For these reasons, the standard of care for tumor diagnosis is a combination of clinical presentation, ocular examination findings, fluorescein angiography, and imaging. Ocular examination in the eye is similar to a gross examination because most of the intraocular structures are visualized using indirect ophthalmoscopy, slit lamp funduscopy, and high-resolution photography. The rapid development of imaging techniques using light wave technology (optical coherence tomography [OCT]) results in high-definition images of the layers of the cornea, the anterior segment, retina and optic nerve, and some tumors. Ultrasonography and fluorescein angiography assess intrinsic qualities of the tumors and vascularization characteristics. High-resolution magnetic resonance is also used for diagnostic purposes in intra- and extraocular tumors. As a result, the pathologic findings usually correlate very well with clinical findings in the most common tumors and ocular diseases.

The challenge for the pathologist is to handle the ophthalmic specimens correctly to obtain adequate correlation of clinical findings with pathologic features and interpret risk for metastasis and other important prognostic factors.

Enucleation, evisceration, and orbital exenteration

Laterality is important in the eye and should be written clearly in the pathologic description and final interpretation (eg, right or left eye). The most common radical resection of an eye is enucleation, which consists of the removal of the eye and a portion of the optic nerve without extraocular tissues (extraocular muscles, conjunctiva, fat, or eyelids). *Enucleations* are performed to remove eyes with tumors or end-stage nonneoplastic diseases that cause blindness and pain. Some of these nonneoplastic pathologic alterations are more often addressed by performing an evisceration of the intraocular contents. *Evisceration* specimens include the cornea with a peripheral rim of sclera and anterior segment structures, the curettage of intraocular contents (choroid, retina, vitreous), and the crystalline lens if present or an intraocular prosthetic lens. The specimen does not include sclera, optic nerve, or extraocular tissues. The most radical resection of an eye is the orbital exenteration, and it is usually performed to surgically remove orbital tumors or intraocular tumors with orbital extension. *Orbital exenterations* contain the ocular globe with the orbital portion of the optic nerve, extraocular tissues (extraocular muscles, adipose tissue, lacrimal gland, conjunctiva), and eyelids. In this chapter we will only address enucleations as these are the most common malignancy-containing specimens received in the pathology laboratory.

I. Indications for enucleation

1. Children with advance retinoblastoma may undergo primary enucleation, especially unilateral cases in which the procedure may be curative. In patients with bilateral retinoblastoma, a primary enucleation may be indicated as one eye may be too advanced (group E of the clinical International Intraocular Retinoblastoma Classification) to be treated with conservative therapies. The other scenario is in patients that have been treated with conservative therapies and had failed and undergo a secondary enucleation. In both primary and secondary enucleations, the pathologist should evaluate high-risk histopathologic features for metastasis and distinguish therapy-related findings when applicable. In unilateral retinoblastoma undergoing primary enucleation, the tumor is usually retrieved fresh for genetic and other molecular studies to exclude a germline mutation. These eyes require special handling that will be discussed below.

2. Patients with uveal melanomas who elect enucleation, those that are not candidates for radiation brachytherapy, or those that have failed brachytherapy are treated with enucleation. Fresh tumor harvesting in primary enucleated eyes with melanoma is performed for molecular prognostic testing.

3. Other ocular tumors may necessitate enucleation as no other options are available for treatment; they include medulloepithelioma, ciliary body tumors (adenoma, leiomyoma), retinal astrocytoma, hemangioblastoma, optic nerve glioma, advance meningioma, cornea/conjunctiva squamous cell carcinoma invasive into intraocular structures, and bulbar conjunctiva melanoma with intraocular invasion.

4. Blind painful eyes usually as a result of chronic nonneoplastic pathologies, such as congenital anomalies, glaucoma, retinal detachment, uveitis, trauma, or complications of intraocular surgeries, undergo enucleation. Patients with severe infectious panophthalmitis may be treated with enucleation.

II. What do we expect to see in the enucleation specimen macroscopically and microscopically?

In the enucleated eye with tumor, it is important to orient the eye adequately to obtain a complete section through the ocular structures and the tumor.

Based on the above indications, the goal is to identify the layers of the eye that are invaded by tumor (Figure 43-1). For retinoblastoma, the level of invasion in the optic nerve determines prognosis. Postlaminar (lamina cribrosa) optic nerve invasion (PLONI) in most cases implies adjuvant chemotherapy for the patient because the probabilities of recurrence in the central nervous system (CNS) increase from less than 10% to up to >80% depending on the amount of tumor. This underscores the importance of adequate grossing and sectioning of the eye to obtain sections through the optic nerve. The optic nerve is the surgical margin in retinoblastoma and should be inked and a cross-section submitted for evaluation. Choroidal invasion and scleral invasion with extraocular extension is also important to evaluate. To adequately evaluate these features, serial cross-sections of the calottes (caps of the eye after obtaining the central section, see below) are necessary. In melanoma the tumor exits the eye through the vortex veins and directly through the emissary channels into the extraocular orbital tissues. The surgical margins in melanoma include the four vortex veins that are taken before opening the eye. Melanoma usually does not invade directly the optic nerve, and this margin is not necessary to take in these tumors (Figure 43-2).

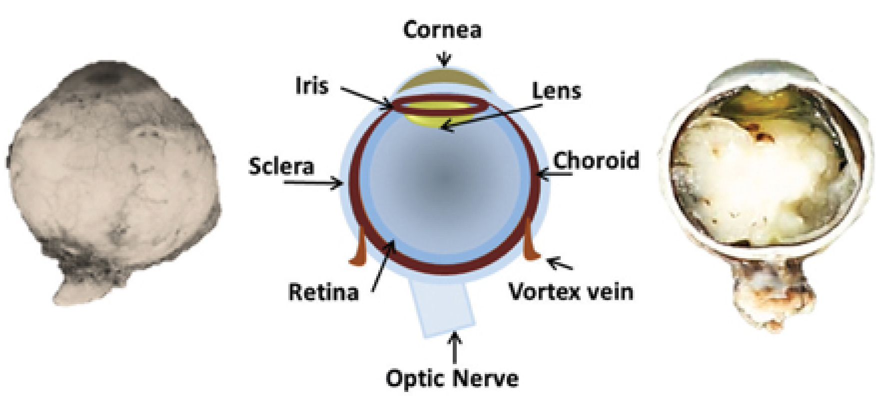

Figure 43-1. Enucleated eye. B. Ocular structures. C. Sectioned eye with retinoblastoma.

III. Typical gross photos of enucleation specimens

Gross diagnosis based on macroscopic observation is critical, particularly in noting areas with different appearances and submitting them for microscopic examination. Correlation with the microscopic findings will dramatically enhance the diagnostic accuracy. See Figures 43-2 and 43-3.

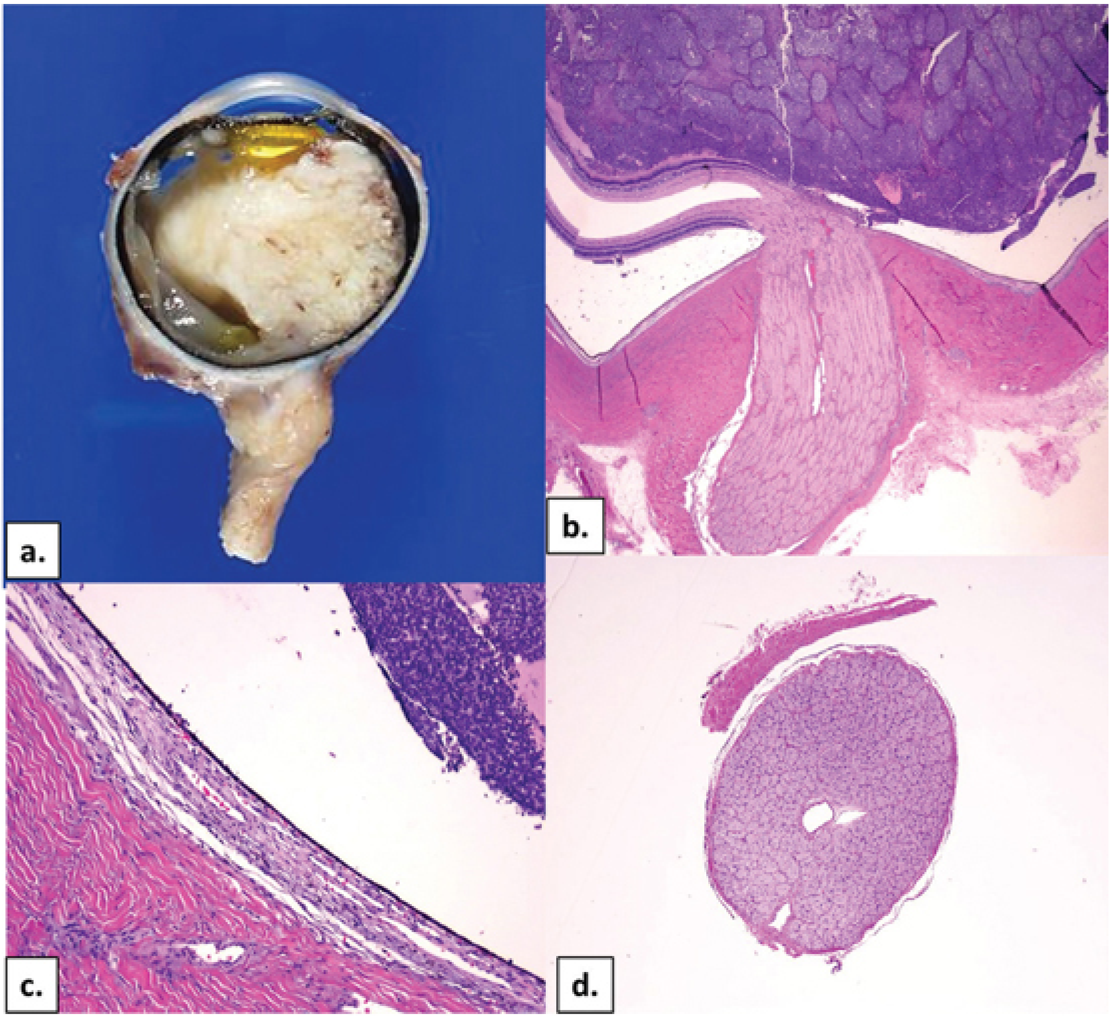

Figure 43-2. Enucleated eye with retinoblastoma. A. Gross picture of the pupil-optic nerve (PO) section shows anteriorly the open anterior chamber and transparent lens (usually seen yellow after fixation). The tumor is tan-white, with congested blood vessels and calcifications seen as bright white areas. The tumor is exophytic (growing from the retina towards the choroid) and predominantly growing as a single tumor. The reminder of the retina is partially detached. The detached retina and the tumor cover the optic nerve head. B. Histopathologic section of the grossed eye with a low-power view of the posterior pole with the optic nerve in the PO section. Notice that the optic nerve is complete showing the prelaminar optic nerve head (partially cover by the retina) with the exophytic tumor but without tumor invasion. The lamina cribrosa and postlaminar optic nerve regions are free and show the central vessels in most of the section. The tumor shows areas of necrosis and subretina seed at the far right. C. Histopathologic section of the calotte and medium power view of the sclera (eosinophilic collagenous layer, inferior left), choroid and retinal pigment epithelium (RPE) layer (pigmented) and the tumor (top right) without tumor invasion into the choroid. D. Cross-section of the optic nerve margin shows the central artery and vein and portions of the dura without tumor.

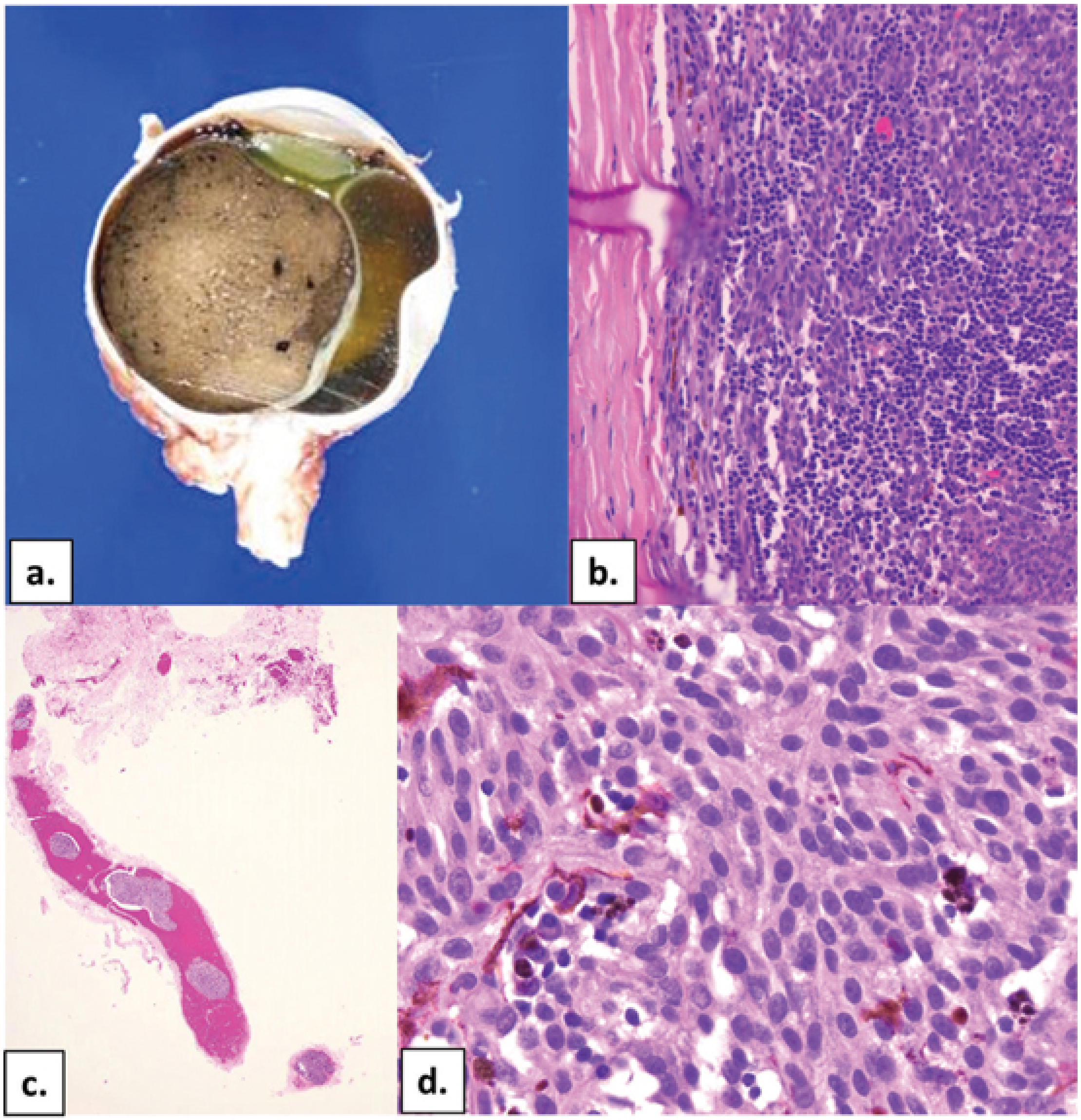

Figure 43-3. Enucleated eye with uveal melanoma. A. Gross picture of the pupil-optic nerve (PO) section that shows anteriorly the open anterior chamber and mildly opaque lens (usually seen yellow after fixation). The tumor is tan-brown with darkly pigmented areas and nodular growth (in the choroid). The retina is completely detached with associated subretinal gelatinous exudate (yellow-brown exudate to the right of the white detached retina). B. Histopathologic section of the eye at the posterior pole in the equator shows the sclera to the right and the tumor focally invading the sclera with lymphocytic infiltrate at its base. C. Histopathologic section of the vortex vein shows tumor thrombi. D. High-power view of the tumor shows mostly amelanotic spindle-type melanoma with few pigmented tumor cells and pigment-laden macrophages. Foci of lymphoplasmacytic infiltrate are also seen.

IV. Dissection techniques: step by step description

1. Material, instruments, and special handling for grossing ocular specimens: To facilitate the adequate handling of ocular specimens, the use of a stereoscopic microscope is recommended. Ideally this would have a camera to record the findings when necessary. A ruler and a Vernier (short scale) are necessary to adequately measure the dimensions of the spherical eye. A pair of scissors, forceps, and a free-hand sharp blade not attached to a handle is better to avoid dragging of intraocular tissues at time of sectioning. A set of color pencils is useful for marking landmarks and retroillumination shadows.

2. How to orientate ocular enucleation specimens: The goal for orientation of the eye is first to confirm laterality of the specimen and second to adequately interpret diagnostic findings. The anterior surface contains the cornea and the insertion of the four rectus muscles in the sclera a few millimeters from the limbus. The posterior surface has the optic nerve and the insertion of the inferior and superior oblique muscles in the

temporal hemisphere. The temporal hemisphere of the eye is slightly larger than the nasal because the optic nerve exits the eye about five degrees into the nasal hemisphere.

The eye is oriented by locating the insertion of inferior oblique muscle on the posterior surface (Figure 43-4). Of the six extraocular muscles, the inferior oblique inserts temporally (lateral) to the optic nerve and its nasal inferior tip is behind the macular region of the retina. To find its insertion it is helpful to identify first the posterior long ciliary vessels and nerves that run horizontally just beneath the sclera and appear as light blue lines to each side of the optic nerve. The insertion of the inferior oblique is usually slightly inferior to these vessels. The muscle inserts directly into the sclera without tendon, and the muscle fibers run from superior to inferior and from temporal to nasal in an oblique pathway. In contrast, the superior oblique inserts directly superior temporal to the optic nerve and behind the superior rectus muscle with a long tendon insertion. After locating the insertion of the inferior oblique, then the orientation would be of a right eye if the inferior oblique is located temporally (right; as seen in Figure 43-4) to the nerve or of a left eye if the insertion of the inferior oblique is located nasally (left) to the nerve.

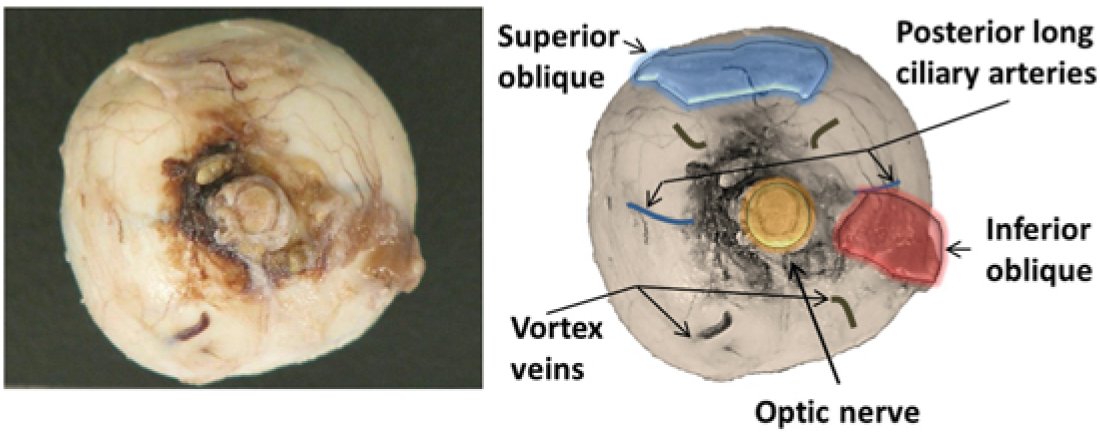

Figure 43-4. Orientation of the eye for laterality from the view of the posterior surface.

To avoid having to continuously check this orientation during grossing, a mark at 12:00 o'clock running from the limbus to the optic nerve on the sclera is performed with a colored pencil. To locate and describe structures or lesions in the eye, the clock hours are used. A different color maybe used to delineate the shadow of the tumor during transillumination.

3. Resection margins: The resection margins are the conjunctival limbal margin, the entire surface of the sclera, the segments of muscle attached to the eye, the vortex veins, and optic nerve cut margin. The margin taken for microscopic examination depends on the type of tumor the eye contains. See below.

Retinoblastoma: The optic nerve margin is the margin to evaluate in eyes harboring retinoblastoma. Retinoblastoma tumors have an affinity to invade the optic nerve, and they may track the nerve and/or the meninges into the intracranial nerve and tissues. The margin should be obtained before opening the eye to avoid carrying tumor into the tissue, causing an artifactual tumor presence in the tissue.

Before taking the margin for histologic examination, the measurement of total length of the optic nerve is taken, then the margin is inked, and a cross-section about 3 mm to 4 mm thick is obtained. The margin is accessed at permanent sections, although a touch imprint of the fresh cut surface may be obtained for rapid assessment. The touch imprint usually shows blood and meningothelial cells. The findings would not change the surgical procedure, as the distal nerve retracts into the apex of the orbit or into the intracanalicular space and it is not feasible for the surgeon to try to get more margin. If the tumor is at cut margin it has already seeded into the orbital tissues.

Uveal melanoma: Melanoma metastasizes through the vessels, and the four vortex veins are the margins assessed in the eyes with choroidal melanoma. The veins are located slightly posterior to the equator in the superior-temporal, inferior-temporal, inferior-nasal, and superior nasal positions (Figures 43-1, 43-3, and 43-4).

The veins are taken by gently pulling the vein and closely cutting with scissors at the exit of the vein from the sclera. The veins should be obtained before opening the eye fresh for tumor retrieval to avoid artifacts of the procedure. If the vein is thrombosed by tumor, it would be rigid, and it can be seen or palpated.

Other tumors: Conjunctival squamous cell carcinoma and melanoma would require assessing the conjunctival margins. These margins are inked and taken for permanent sections.

4. Fresh tumor retrieval: Genetic testing may be necessary in patients with unilateral retinoblastoma to exclude a germline mutation (hereditary form), and fresh tumor is required. In patients with melanoma, molecular tests are used in prognostication of metastatic potential of the tumor, and fresh tissue is preferred. In both scenarios, prompt handling of the eye after enucleation is necessary to avoid degeneration of tumor. In some practices, the ophthalmic surgeon would retrieve the tumor at the operating room, and thus the eye will arrive to the pathologist already opened. We describe here the procedure to retrieve tumor by the pathologist. The tumor and extraocular fibrous adipose tissue (as nontumor tissue control) are harvested and immediately frozen at -70°C. It is recommended to at least have three samples from each type of tissue obtained for backup and possible future research material.

Additional material required for fresh tumor harvesting includes: two sets (one for the tumor and one for the normal tissue) of sterile forceps and scissors, a suture removal kit may be used. Cryovials labeled with surgical pathology number/last name of patient and Tumor or Fat to put the tissue and snap freeze in a cryobath. Sharp blades to open the eye. Slides and alcohol to fix the touch imprints at time of optic nerve margin sectioning (see above) and for the touch imprints of tumor (quality control of tissue submitted for molecular testing).

a. Retinoblastoma: After orienting the eye for laterality and obtaining the optic nerve margin as described previously, the eye is transilluminated to evaluate size and location of the tumor.

A strong focused light (halogen is usually used) source is necessary. The lights from the stereoscopic microscope can be used for this purpose. It is recommended that the room lights be dim so that the shadow in the eye is better seen at time of transillumination. The source of light is usually positioned in front of the cornea (Figure 43-5A-C), and the eye is gently turned to locate the shadow. If the tumor is not large, then the light may shine through the eye until the eye is positioned with the shadow in front of the light (Figure 43-5A,B). When the shadow is seen, a color pencil or a marker can be used to delineate the shadow (Figure 43-5C). In cases of large tumors that occupy the entire posterior pole, there is no transillumination and no marking is necessary. The scleral window to obtain tumor should be done at the edge of the shadow (Figure 43-5D) with a sharp blade (see below) with the purpose of keeping most of the tumor untouched and incorporated in the future pupil-optic nerve (PO) section. After fixation, the eye will be sectioned to obtain the PO and the two calottes that in this example are inferior and superior (Figure 43-5E). The scleral window will be present in one of the calottes and not in the PO section.

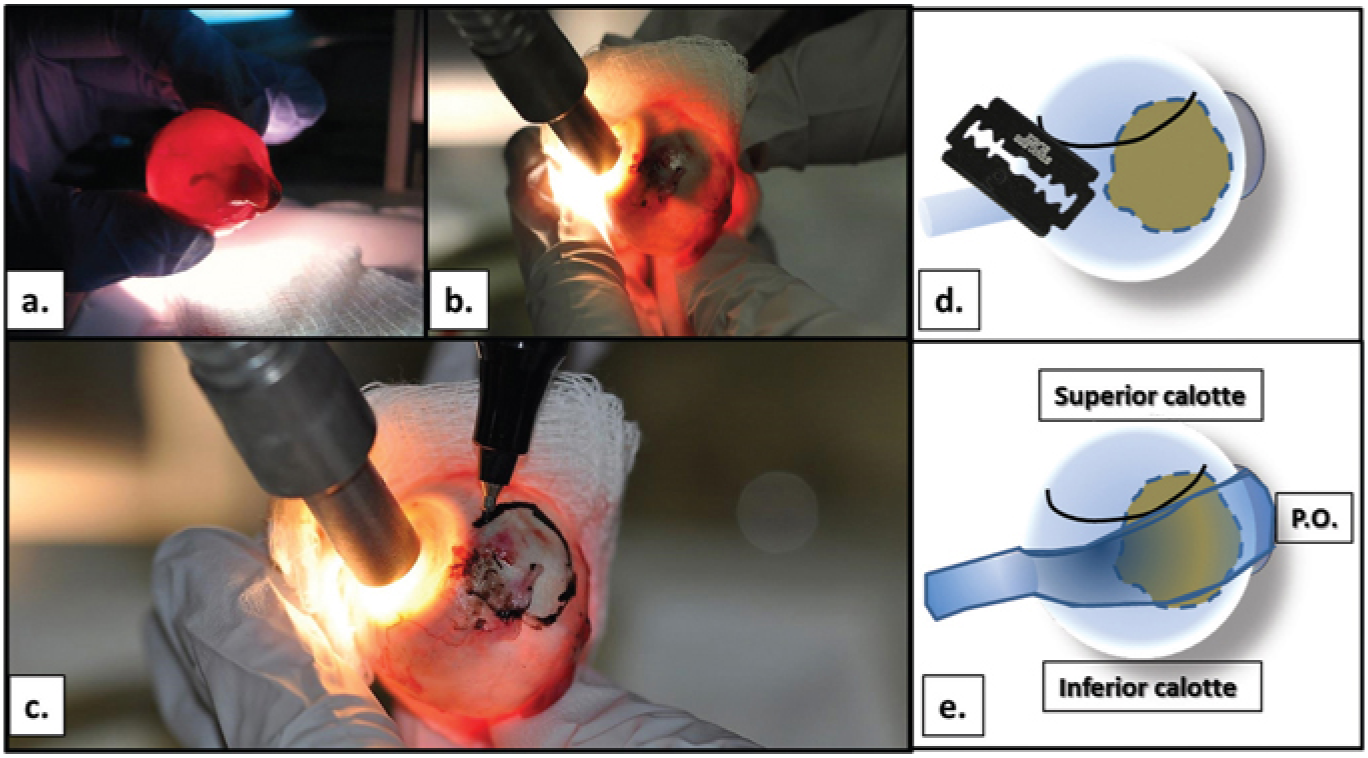

Figure 43-5. Transillumination of an eye with tumor and orientation for sectioning for tumor retrieval.

After the scleral window is created, the tumor is closely inspected under the stereoscopic microscope to select the area for harvesting. Areas without extensive necrosis, large calcifications, retinal pigment epithelium, or retina/choroid tissue are selected. The selected areas are retrieved either by cutting with the scissors and then handling them with the forceps or directly with the forceps as the tumor is very friable. The tumor is then placed in the cryovial. To confirm that the tumor is mostly viable, a small piece of the same area is placed on a slide (using another slide to smear on a monolayer) and stained with a rapid hematoxylin-eosin (H&E) stain and microscopically check viability of cellularity. After harvesting, the eye is placed in adequate amount of formalin (at least five times the volume of the eye) and gently moving the eye so the opening is on top and the formalin enters the eye and reforms its shape.

b. Uveal melanoma: Fresh tumor harvesting in uveal melanoma is very similar to retinoblastoma. The difference is to obtain the vortex veins as margins before opening the eye instead of the optic nerve. The tumor is in the choroid and not in the retina, and it may require cutting it with small scissors because melanomas are more cohesive and difficult to just grasp with the forceps. One should take care of not disrupting the overlying retina or the sclera.

5. Fixation: Eyes that have been open for tumor retrieval need only 24 to 48 hours of fixation. Those eyes that are directly placed in formalin without fresh tumor retrieval are usually fixed for more than 48 hours to 5 days to assure adequate penetration of formalin into the intraocular structures and tumor. There is no need to open the cornea or inject formalin into the eye, and this practice should be avoided as this may alter the intraocular structures and interpretation of findings by inadvertently dragging tumor into other structures.

6. Measurements: After the eye is oriented for laterality (see Figure 43-4) the eye is measured with the Vernier to obtain the three dimensions: anterior-posterior (tip of cornea to posterior sclera adjacent to optic nerve), and horizontal and vertical diameters (at the equator of the globe). The shadow from a tumor seen under transillumination is also measured for its maximum diameter. The distance from the limbus to the edge of the shadow and the distance from the optic nerve to the edge of the shadow are also measured. The location of the shadow is further defined by describing between which clock's hours the shadow is seen when the eye is seen from the front. The length of the optic nerve is measured from the sclera to the tip of the optic nerve, and the diameter of the optic nerve is measured at the portion just distal to the sclera. The cornea's horizontal and

vertical dimensions are measured from limbus to limbus. The diameter of the pupil is also recorded. Any lesion in the surface of the eye (conjunctiva, cornea, or sclera) is described, and three dimensions are measured. After sectioning, the tumor's base dimension at the cut surface is measured and the height at cut surface and maximum height. This is especially important for the uveal melanoma as it is part of the staging.

7. How to section the globe: The default sectioning of the eye is on the horizontal plane to include cornea, pupil, lens, macula, and optic nerve in the PO section. In this plane the resulting calottes are superior and inferior (Figure 43-6B). However, when a tumor is present in other sites not in the horizontal plane, then the decision of how to cut the eye rests on where the tumor is present (Figure 43-6A,C). The eye is then positioned with the region of the eye that will be removed first to be in the top (superior) in relation to the cutting board surface. When a scleral window has been created to retrieve fresh tumor, this window should be included in one of the calottes to allow for an intact PO section (Figure 43-6D). The cutting board surface should be covered with a piece of gauze or cloth so the eye would not slip or move during the sectioning. Then the eye is approached from the back to start the section at about 0.5 mm superior to the optic nerve into the sclera. It is important to use a sharp and thin blade to avoid dragging intraocular tissues with the sectioning. The blade is firmly held against the eye while the eye is maintained firmly in position using the opposite hand by positioning the index or index, middle fingers, and the thumb on the top equator of the eye (Figure 43-6E). The initial movement is pushing forward into the sclera and with short lateral movements to penetrate the sclera. When the sclera is penetrated, then the pushing forward should be subtle and the lateral movements longer and precise, so the tissues are not dragged inside. This process is repeated until the blade reaches past the equator about 5 mm to 6 mm from the limbus (Figure 43-6F,G). At this point when the ciliary body and lens will be almost reached, it is advisable to check the position of the blade in relationship with the expected corneal entry of the blade. This should be about 1 mm to 2 mm from the limbus into the clear cornea (Figure 43-6H). The eye is then turned on the corneal surface down and, using now both hands, a firm, quick, guillotine-like movement of the blade is made to avoid dragging the lens into the anterior chamber and sectioning the lens and cornea with a clean cut (Figure 43-6I). This results in a calotte and the rest of the eye with the optic nerve and central portion of the eye. The cut surface is examined and described, and then the other calotte is obtained by repeating the same procedure (Figure 43-6J,K). The resulting sections are the two calottes and the central PO section (Figure 43-6L).

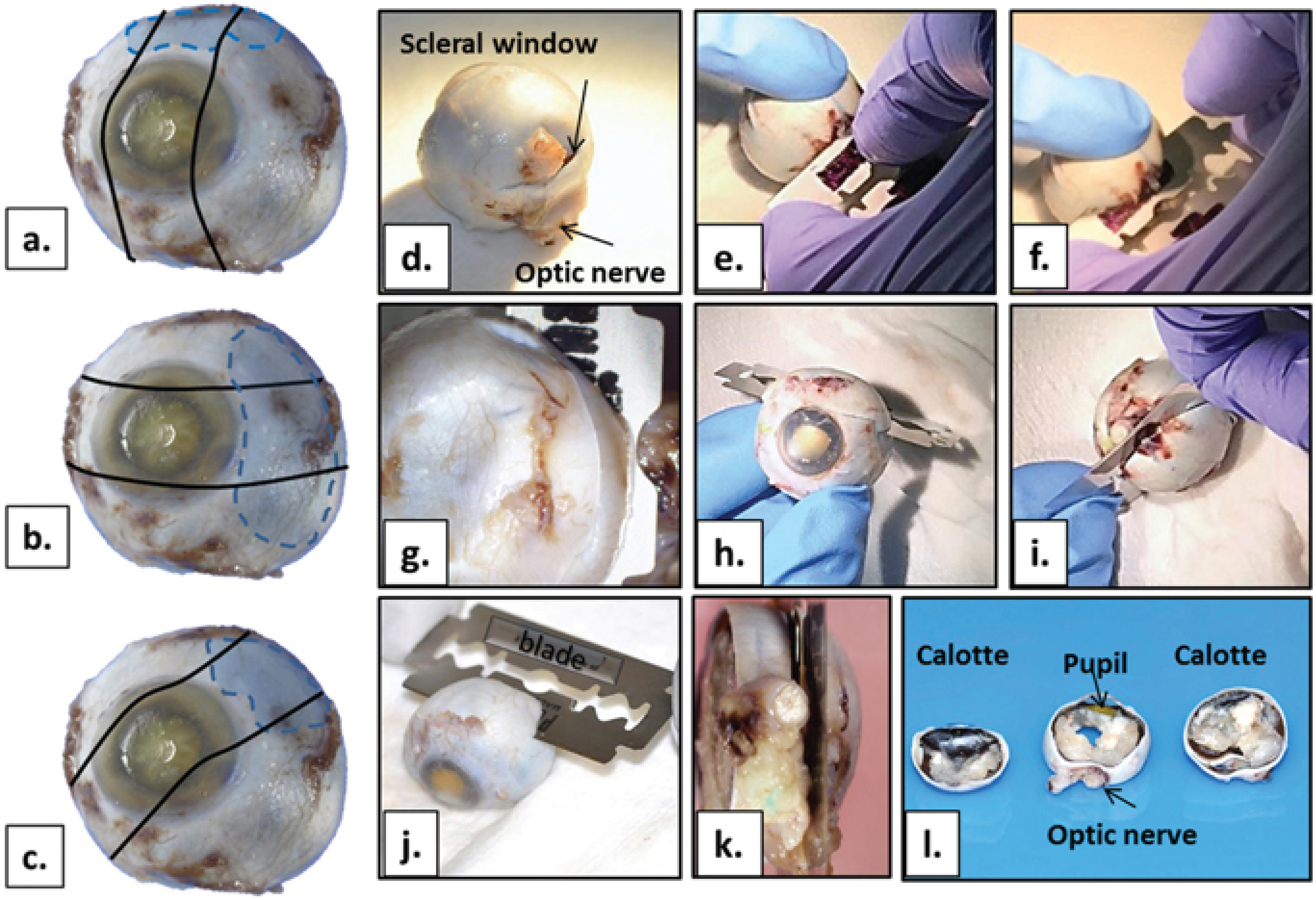

Figure 43-6. Macroscopic examination and sectioning of the eye with tumor.

The calottes are then further sectioned in an anterior-posterior direction, in a bread-loaf fashion (Figure 43-7A,B). The entire eye is then submitted, calottes on edge, for histologic examination in four cassettes (Figure 43-7C).

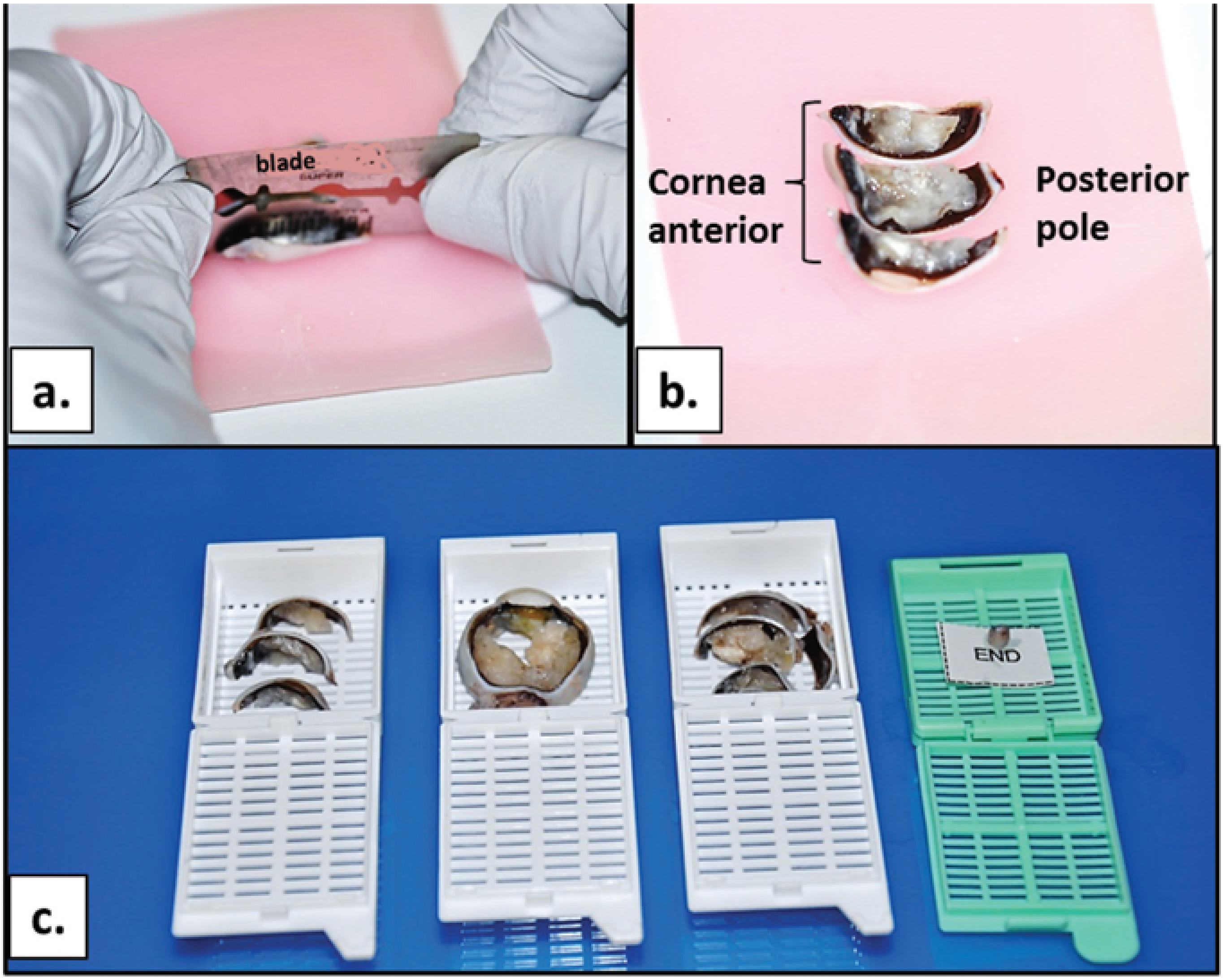

Figure 43.7. Sectioning and submitting tissue for processing.

8. Description of findings after sectioning the eye.

The description should center on the main pathology or neoplasia and its relationship with ocular structures (please see specifics for each tumor below). The anterior segment structures, status of the anterior chamber angle, iris, lens, ciliary body, vitreous, retina, optic nerve head, choroid, and sclera are described for the presence of lesions, tumor, or no pathologic alterations.

a. Retinoblastoma: In retinoblastoma the prognosis for cure by enucleation or possible recurrence depends strongly on the presence or absence of extraocular extension of the tumor. Thus, the pathologist should carefully access any invasive component of the tumor. On external examination of the eye, description of any extraocular extension of tumor is carefully documented and measured. After sectioning the eye, description of the location of the retinoblastoma mass in relation to the retina is important to access growth pattern that is associated to some risks for extraocular invasion. If the tumor is growing into the vitreous cavity, this represents an endophytic tumor and is associated to development of vitreous seeds that can land in the optic nerve and invade the optic nerve and possibly the central nervous system (Figure 43-5B,D). The exophytic growth pattern is when the tumor grows from the retina into the subretinal space towards the choroid (Figure 43-5A). This type is associated with choroidal invasion and possible extraocular extension through the sclera. Many cases have a combined endophytic and exophytic growth pattern and may present with choroidal invasion and vitreous seeding (Figure 43-5C,E). The base of the tumor in contact with the choroid/sclera is measured as well as the maximum height. These measurements are no longer required for the American Joint Committee on Cancer (AJCC) 8th edition staging. The color of the tumor, the extent of necrosis and calcification, vascularization, and

hemorrhage are also described. In addition to the tumor characteristics, the status of the anterior segment is described, especially if there are peripheral anterior synechia of the iris, neovascularization of the iris, and obliteration of the anterior chamber angle (Figure 43-5E).

b. Melanoma: In melanoma the external examination before sectioning should include description and measurement of any tumor extension through the vortex veins or sclera (Figure 43-6). It is also important to describe any scleral melanocytosis as some melanomas are associated with primary melanocytosis. After sectioning, the tumor location and extend of involvement in the uveal tract is described (choroid or/and ciliary body or/and iris). In uveal melanomas the size (at base and in maximum height) has a prognostic value and it is part of the AJCC staging and should be measured carefully. Description of the shape (dome, mushroom, diffuse, partially necrotic) of the tumor and the invasion into the subretinal space, retina, vitreous ,or sclera should be noted (Figure 43-6).

c. Other (anterior segment tumors, medulloepithelioma): In any other tumors the size, color, consistency, and location of the tumor and invasion into the adjacent structures, especially extraocular and into the optic nerve, should be noted.

9. Photographs: Gross photographs are obtained of the eye before opening from the front and back and including any pathologic findings of the ocular surfaces. After sectioning the eye, photographs are obtained of the central PO section and calottes, with especial attention to the relationship of the tumor with the intraocular tissues.

V. Gross descriptions using paragraph system

1. The first paragraph of the gross description includes: If the eye was received fresh or fixed in formalin; laterality; and the integrity, shape, and consistency (soft, firm) of the eye are described. If the eye is received fresh for tumor retrieval, then describe site where the scleral window was created and that the tumor was sent for genetic studies and/or tumor bank. Then the measurement and description of the eye structures (see above) are noted.

2. After sectioning. Description of the anterior chamber, lens, and ciliary body should be at the beginning of this paragraph. The last part of this paragraph is the status of the structures of the posterior pole and sclera, optic nerve that are not involved by tumor.

3. Tumor characteristics. In this paragraph the tumor characteristics with location and associated invasion into the ocular and extraocular structures are described (see above for specific features for retinoblastoma and melanoma).

Ink code: Optic nerve margin is inked. Any areas of extraocular extension should be inked, and if there are more than one site, then designate the ink color for each site.

Section code:

A1: Pupil optic nerve section

A2: First calotte obtained, segments on edge

A3: Second calotte obtained, segments on edge

A4: Optic nerve margin on end (for retinoblastoma)

A4-7): Vortex veins (superior temporal; inferior temporal; inferior nasal; superior nasal) (wrapped in paper); one per cassette (for melanoma)

A8: Any additional lesions

VI. Common pathologic findings in enucleated eyes

Based on the indications for enucleation for retinoblastoma:

1. Complete PO section with adequate optic nerve to evaluate invasion in all the parts of the optic nerve (Figure 43-2B).

2. Percentage of tumor necrosis and necrosis of intraocular structures if present (>90% carries higher risk of concomitant invasion of the optic nerve and choroid) and presence of calcifications.

3. Tumor degree of differentiation (retinocytoma to poorly differentiated). Moderately differentiated tumors have rosettes, either Flexner-Wintersteiner (F-W) or Homer Wright (HW) or both.

4. Degree and amount of anaplasia.

5. Vitreous seeds (type: dust, sphere, and/or cloud).

6. Invasion into optic nerve (prelamina cribrosa, laminar, postlaminar, at cut end, in meninges) and status of optic nerve margin. Measurement of maximum depth of optic nerve invasion can be taken from inner limiting membrane of the optic nerve or when this area is obliterated by tumor from the level of Bruch's membrane to the deepest point of invasion (Figure 43-2B,D).

7. Invasion into choroid (less than 3 mm in maximum diameter; 3 mm or more in maximum diameter; or multiple foci of choroidal invasion that adds to 3 mm or more tumor invasion) (Figure 43-2C).

8. Invasion into sclera (direct or perivascular/neural through the emissary channels into inner half, outer half but not reaching the episclera, episclera, or overt extraocular extension).

9. Signs of previous treatment effect.

Based on the indications for enucleation for uveal melanoma:

a. Complete sections with adequate uveal tract and complete sclera (Figure 43-3A). Often the calottes that show more choroidal and scleral surface contain the features of invasion.

b. Assessment of degree of invasion into retina and extraocular tissues.

c. Type of cellularity (spindle A, B, or/and epithelioid) and percentage of each in the tumor.

d. Mitotic count per 40 high-power fields.

e. Presence or absence of vasculogenic mimickers (better seen using periodic acid-Schiff stain).

f. Intravascular vortex vein invasion (Figure 43-3C).

g. Degree of necrosis and pattern of growth (diffuse).

h. Involvement of ciliary body.

VII. Common potential staging pitfalls and solutions

For retinoblastoma the potential staging pitfalls and solutions include:

1. Incomplete optic nerve sections that preclude evaluation of the lamina cribrosa region.

Solution: Ask histotechnician to get early sections of the pupil-optic nerve section to make sure you get the edge of the optic nerve (about 20 levels - stained 10). Then obtain another 20 levels (10 stained with H&E) of the region of the optic nerve; thus, you will be sampling the nerve at the periphery and center. The histotechnician can always get deeper levels if the nerve is still incomplete.

2. Floaters of retinoblastoma tumor in the choroidal spaces, meninges, or episclera mimicking tumor invasion.

Solution: True invasion of these structures expands the tissue by solid tumor with focal central necrosis if any. The floaters usually are made of small pieces of tumor with central solid tumor and surrounded by necrotic tumor. They do not distend the tissue but rather they occupy the space already there in the tissues.

3. Misinterpretation of other choroidal pathology as tumor invasion.

Solution: Recognize other pathology such as extramedullary hematopoiesis, chronic inflammation, and small hemangiomas as possible findings in these eyes. Immunohistochemistry using synaptophysin is useful in these cases as the tumor is positive, while the other pathologic entities are negative for synaptophysin.

4. Not identifying massive choroidal invasion or extraocular extension of tumor when only the PO section is included.

Solution: Always submit for embedding the two calottes in segments so there is more choroidal and scleral surface to examine and thus identify potential invasion.

5. Overcalling subretinal pigment epithelial invasion for choroidal invasion.

Solutions: Recognize that the sub-RPE space is still part of the retina and not the choroid, thus unless the tumor has broken through Bruch's membrane into the choriocapillaries layer it is not in the choroid.

For uveal melanoma the potential staging pitfalls and solutions include:

1. Incomplete sections of the uveal tract where potential scleral or vascular invasion may be present.

Solution: Always submit for embedding the two calottes in segments so there is more choroidal and scleral surface to examine and thus identify potential invasion.

2. Overlooking the epithelioid component of the tumor.

Solution: Review carefully representative sections of the entire tumor in the PO and in the calottes.

3. Overcalling scleral melanocytosis for extraocular extension of tumor.

Solution: Be aware that patients with melanoma may have increase melanocytes in the sclera and perivascular locations other than the choroid. These melanocytes are dendritic and smaller than melanoma cells.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

- Heading of the report should start with the structure excised and laterality (right or left eye) and procedure (enucleation).
- Describe type of tumor – retinoblastoma or melanoma and type of differentiation
- Type of tumor growth, include any degree of necrosis in percentage relative to the tumor mass, the presence of rosettes in retinoblastoma and amount of epithelioid melanoma cells in melanoma, and the tumor size for melanoma
- Where is the tumor invasion: in retinoblastoma - choroid and amount in millimeters at the base and height; optic nerve up to which level and depth of invasion in millimeters. In uveal melanoma - invasion into or through the sclera or by intravascular permeation, or into the retina and optic nerve.
- Tumor invasion of extraocular tissues, extent.
- Status of the margins: For retinoblastoma: the optic nerve cut end and if extraocular extension present the soft tissues/conjunctiva. For uveal melanoma: status of vortex for tumor – intraluminal or perivascular, intrascleral or extraocular.
- Is the tumor unilateral or bilateral, sporadic or familial (if known).

A demo report with its corresponding demo synoptic report is provided below to demonstrate the necessary information to be included in a pathology report, and a synoptic template in a case of retinoblastoma.

FINAL DIAGNOSIS:

Left eye, enucleation

- Retinoblastoma, moderately differentiated with endophytic growth pattern
- 50% necrosis
- Calcifications present
- Postlaminar optic nerve invasion, 5 mm deep from Bruch's membrane
- Massive choroidal invasion (5.5 mm in maximum diameter - two foci [3 and 2.5 mm])
- Vitreous tumor seeds, dust and spheres
- Focal retinal detachment
- Optic nerve margin free of tumor.

Synoptic report

The following information is a modification of the AJCC cancer staging protocol and College of American Pathologists cancer staging checklist for retinoblastoma.

Procedure: Enucleation, eye

Laterality: Right

AP diameter: 23 mm

Horizontal diameter: 22.5 mm

Vertical diameter: 22 mm

Length of optic nerve: 13 mm

Diameter or optic nerve: 4.5 mm

Site of tumor by transillumination: all quadrants

Size of tumor after sectioning:

Greatest basal diameter: 47 mm
Greatest thickness: 3.5 mm
Tumor site after sectioning: All quadrants
Tumor involvement of other ocular structures: Choroid, vitreous and optic nerve
Growth pattern: endophytic
Extent of optic nerve invasion: Postlaminar (5mm from Bruch's membrane)
Histologic grade: G2 (moderately differentiated)
Margins: Negative
Pathologic stage classification (pTNM, AJCC 8th Edition):
  Primary tumor: pT3b
  Regional lymph nodes: N0
  Distant metastasis: M0
Hereditary trait: HX
Pathologic stage: I
Additional pathologic findings: Retinal detachment and Azzopardi's phenomenon

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44. Extragonadal Germ Cell Tumors

Shelley Caltharp, MD; Heather Rytting, MD; Beverly Rogers, MD; Hong Yin, MD

The World Health Organization (WHO) classification of germ cell tumors is generally used for characterization of extragonadal germ cell tumors (EGCTs) and includes the following categories: dysgerminoma/seminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, choriocarcinoma, teratoma, and gonadoblastoma.[1] The prevalence and prognosis of EGCTs is age dependent.[2] EGCTs are relatively common in neonates while rare in childhood (prepubertal) and adults. Worse outcomes are generally associated with increasing age, particularly in pediatric populations. Therefore, EGCTs are commonly divided into congenital/neonatal (birth to 6 months), childhood/prepubertal (7 months to 12 years) and postpubertal/adult (>12 years).

Congenital teratomas can occur anywhere along the body midline, within the embryonic germ cell ridge, and common sites include sacrococcygeal, intracranial, mediastinum, head and neck, and retroperitoneum. Most cases of fetus in fetu are regarded as a form of mature teratoma, while mixed malignant GCTs are more frequent with increasing age and can consist of teratoma, yolk sac tumor, embryonal carcinoma, and rarely choriocarcinoma. The mediastinum is the most frequent anatomic site for EGCTs in adults and in this region is characteristically restricted to males.

I. What do we expect to see in extragonadal germ cell tumors macroscopically and microscopically?

EGCTs are heterogeneous and, depending on histologic type of germ cell tumor excised, gross findings will vary. Tumors frequently appear as complex masses with solid and cystic areas and may contain hemorrhage and/or necrosis. Teratomas contain variable amounts of fat, fluid, calcification, and differentiation of tooth, hair, and osseous structures. In pediatric (prepubertal) EGCTs, complete surgical excision is often effective treatment for children, and most specimens will be received as an en bloc resection.[3] Therefore, careful documentation of size, margins, tumor extension, identification, and involvement of adjacent structures is essential. Identifying involvement of the coccyx is important for staging in sacrococcygeal resections.

II. Typical gross photos of extragonadal germ cell tumor resections

See Figures 44-1 to 44-5.

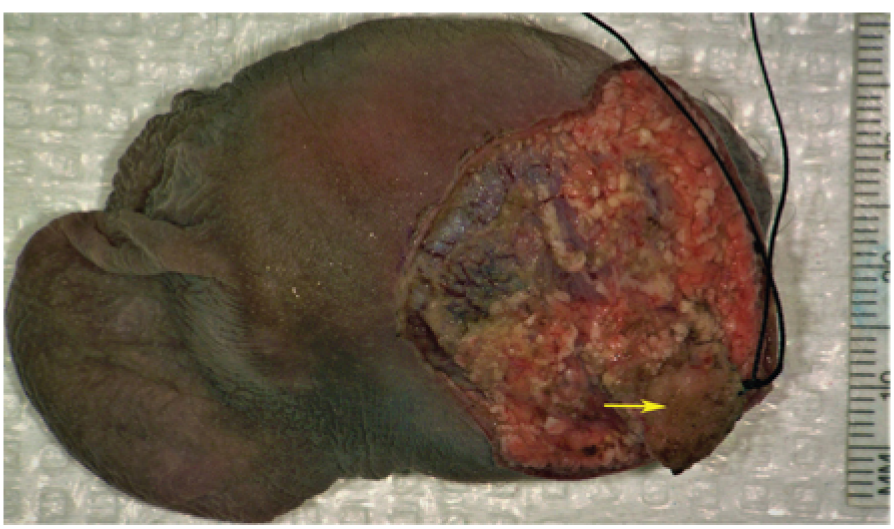

Figure 44-1. Sacrococcygeal teratoma resection. Stitch and arrow marks coccyx.

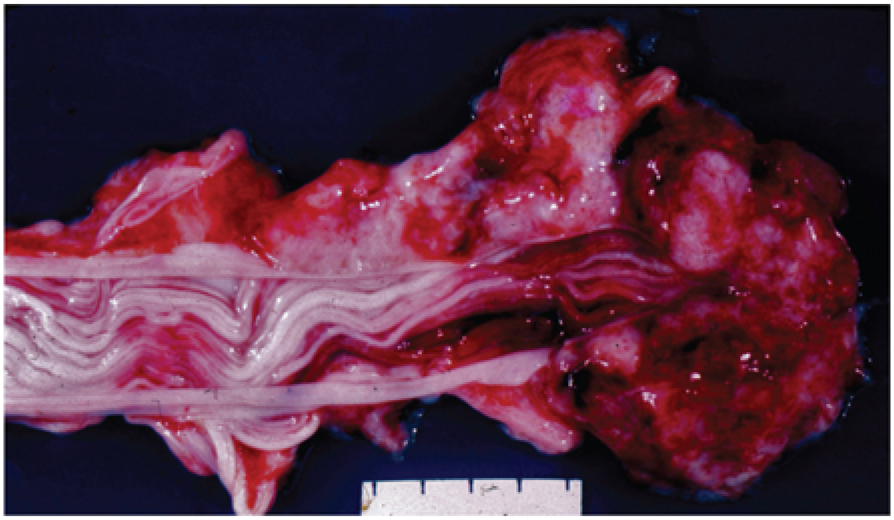

Figure 44-2. Sacroccocygeal germ cell tumor involving spinal cord.

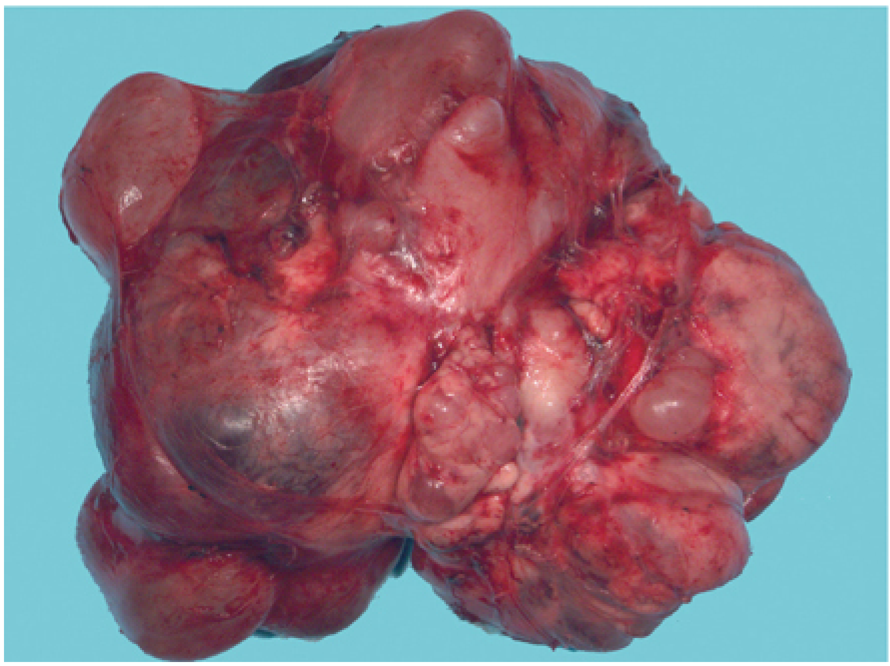

Figure 44-3. External surface of solid and cystic mature teratoma.

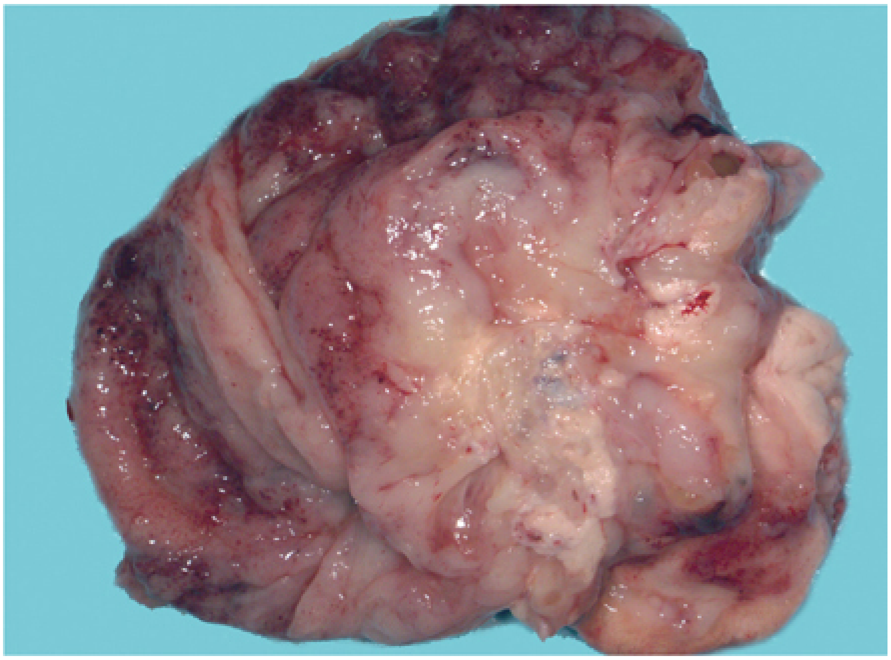

Figure 44-4. Sagittal section (bivalve) of mature teratoma with bone, cartilage, adipose tissue and mature glioneuronal tissue.

Figure 44-5. Postpubertal mediastinal mixed malignant germ cell tumor with teratoma and choriocarcinoma (arrow).

III. Dissection techniques: step by step description

1. Perform close visual inspection of the specimen for orientation, resection margins, and involved attached/adjacent structures. Designation of attached structures, such as the coccyx, is frequently provided by the surgeon with a stitch/ties (for sacrococcygeal tumors, if the coccyx is not visible or unmarked, discuss with surgeon to determine margins). Take gross photographs documenting the external surface, specimen received, and important involved structures.

2. Weigh and measure the main tumor specimen with separate measurements of any involved adherent/attached structures.

3. Prior to opening the specimen, ink the external surface. Spray the surface with an acetic acid solution for color fixation, and evaluate the specimen for possible fluid-filled cystic structures that may need draining. Bivalve the specimen through the long axis. Take gross images documenting the cut surface of the specimen.

4. Tissue banking of gross tumor according to institutional research protocols should be done. Collect fresh tissue to submit or snap freeze tissue for special studies, cytogenetics, or future studies, if warranted.

5. Bread-loaf the specimen perpendicular to initial bivalved cut, and describe and document the findings in the gross dictation. Tumors are usually solid and may have cystic areas. Fix the specimen for several hours or overnight, depending on the size and cellularity.

6. Submit one section/block per 1 cm of greatest tumor dimension. Sample every color and consistency (solid and cystic) particularly paying attention to solid and hemorrhagic areas as extensive hemorrhage is characteristic of choriocarcinoma, and in solid, glial-looking tissue, sample for immature components. Sample tumor with respect to any included/attached structure such as large vessels, muscle, inked resection margins, etc. In sacrococcygeal teratomas, ink the cut coccygeal margin a separate color and submit sections of tumor with respect to coccyx. Submit coccyx entirely, sectioning according to size and for ability to appropriately decalcify.

7. Document gross description, ink code, and section code details as illustrated in section IV below.

IV. Gross descriptions using paragraph system

As previously described, Raymond's paragraph system will be used for gross description.

(A) Pelvic mass: A 38-g soft tissue mass (5.3 x 5.2 x 4.1 cm) with attached coccyx (1.4 x 0.9 x 0.5 cm) marked with stitch. On cut surface the heterogeneous mass contains solid (2.0 x 2.0 x 2.5 cm) and cystic components (2.0 x 2.0 x 2.0 cm). The solid component has a yellow, lobulated appearance without hemorrhage or necrosis and is attached to the coccyx. The unilocular smooth-walled cyst contains clear serous fluid with a small projection of hair. The specimen is inked as follows: black-coccyx; blue - external surface.

Section code

1A: Coccyx with attached mass, entirely submitted (decalcification)

1B-1D: Representative sections of solid component

1E: Representative sections of cystic component

V. Common pathologic findings

1. Mature teratoma
2. Immature teratoma
3. Teratoma with malignant somatic component
4. (Mixed) malignant germ cell tumors

(See Figures 44-6 through 44-8.)

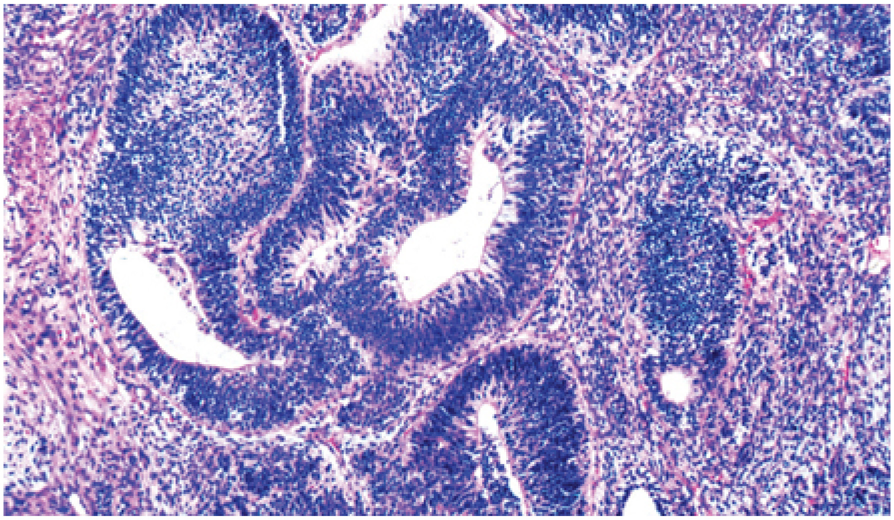

Figure 44-6. Teratoma with immature neuroepithelium (immature teratoma). Histologic grade is based on proportion of tissue containing immature neuroepithelium. Norris grading system: Grade 1 – Occasional foci of immature tissue, neuroepithelium absent or limited to a rare low-power (less than one low-power field (4x) in a given slide); Grade 2 – Greater degree of immaturity with neuroepithelium present in one to three low-power fields in any slide; Grade 3 – Prominent immaturity and four or more low-power fields of neuroepithelium in a given slide.

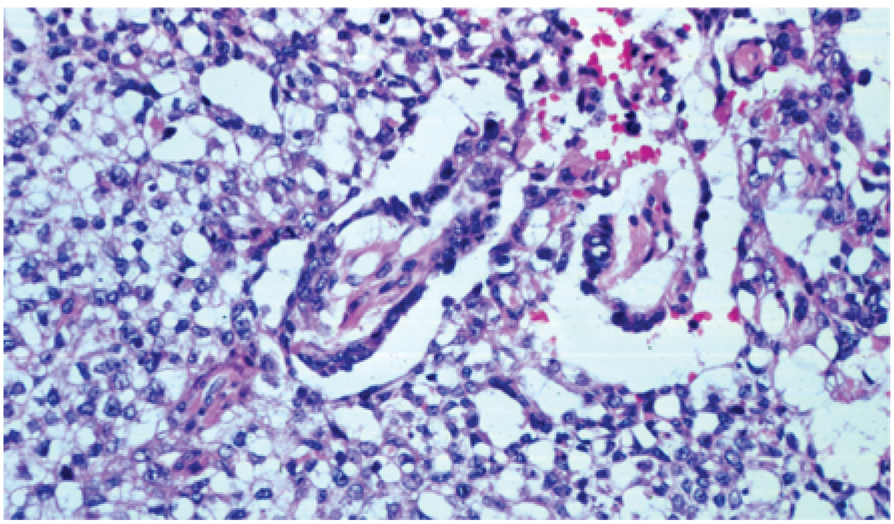

Figure 44-7. Retroperitoneal yolk sac tumor with Schiller-Duval bodies.

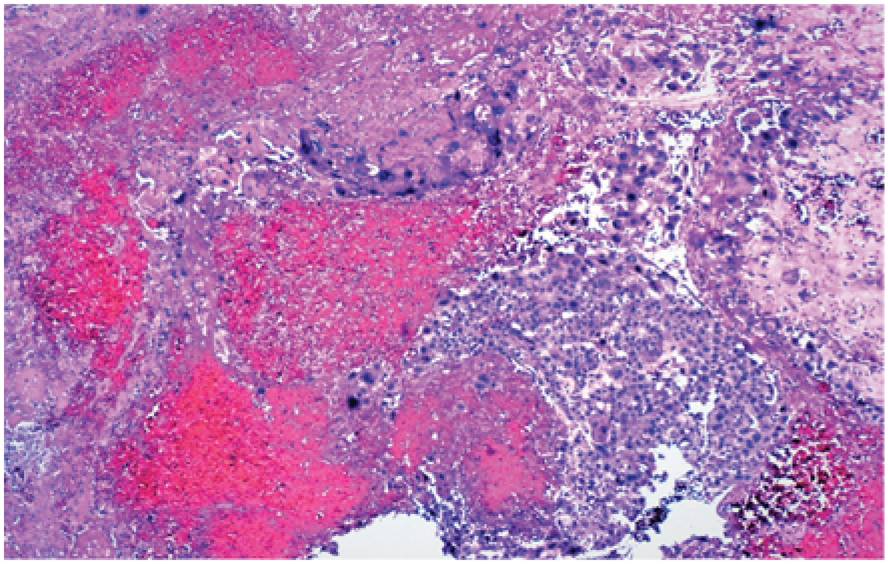

Figure 44-8. Choriocarcinoma within mediastinal mixed malignant germ cell tumor.

VI. Common potential staging pitfalls and solutions

Mixed germ cell elements, including immature teratomatous components, malignant nonteratomatous lesions, or secondary non-germ cell malignancies (in adults), can be minimal and overlooked but are important for prognosis.[4] Furthermore, histologic detection of yolk sac tumor in sacrococcygeal teratomas is important because alpha fetoprotein levels are normally high in the newborn period and therefore may not be reliable for detection of yolk sac tumors. Therefore, in all EGCTs, regardless of location, at least one section per centimeter of the tumor's greatest dimension is recommended.

VII. What to include in the pathology report

- Tumor location, included structures/organs and procedure type
- Tumor histologic type, if mixed germ cell tumor specify components and estimate approximate percentage of each
- If immature component present, indicate histologic grade
- Treatment effect if known preoperative therapy
- If additional organs are resected (ie, sacrococcygeal resection), include tumor extension and involvement of adjacent organs
- Margin status
- Include lymph node status, number submitted and number involved presence of metastasis, if submitted

FINAL DIAGNOSIS

Soft Tissue, Sacrococcygeal, Resection:

- Mixed malignant germ cell tumor (15.0 x 13.5 x 7.8 cm)
  - Mature teratoma (50%)
  - Yolk sac tumor (30%)
  - Immature teratoma, Grade 3 (20%)
- Coccyx uninvolved
- Resection margins free of tumor
- See synoptic report

Synoptic report

The following information is based off the Children's Oncology Group staging system and College of American Pathologists (CAP) cancer protocol for extragonadal germ cell tumors.

EXTRAGONADAL GERM CELL TUMOR: Biopsy, Resection

Procedure: Resection

Wide resection

Patient Age: Congenital/neonatal (birth - 6 months)
Tumor Site: Sacrococcygeal
Tumor Size:
  Greatest dimension: 15.0 cm
  Additional dimensions: 13.5 x 7.8 cm
Histologic Type: Teratoma
  Mature teratoma
  Immature teratoma
  Malignant germ cell
  Yolk sac tumor
Histologic Grade (applicable to immature teratomas only): Grade 3
Percent of teratoma composed of immature elements (if applicable): 20%
Treatment History: No known preoperative therapy
Treatment Effect: No known preoperative therapy (not applicable)
Microscopic Tumor Extension (applicable to sacrococcygeal resections only): Coccyx uninvolved
Margins:
  Uninvolved by tumor
  Distance of tumor from closest margin: 0.2 cm
  Specify margin: Soft tissue
Lymph-Vascular Invasion: Not identified
Perineural Invasion: Not identified
Regional Lymph Nodes:
  No nodes submitted or found
  Number of Lymph Nodes Examined: 0
  Number of Lymph Nodes Involved: 0
Pathologic Staging: Children's Oncology Group Staging for any Malignant Extragonadal Germ Cell Tumors
  Note: COG Staging is based on pretreatment tumor characteristics. Clinical information required to definitively assign stage.
  Stage I: Complete resection at any site; coccygectomy for sacrococcygeal site; negative tumor margins.

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45. Hepatoblastoma

Heather Rytting, MD; Shelley Caltharp, MD; Beverly Rogers, MD; Hong Yin, MD

I. Background

Hepatoblastoma, although rare (incidence one per million children), is still the most common malignant primary liver tumor of infancy and early childhood. Most are diagnosed in the first 2 years of life. Less than 10% are diagnosed after age 5.[1] They can be multifocal, but most are unifocal. Portal and hepatic vein involvement is common, while spread to lymph nodes is less common. Approximately two thirds are unresectable at diagnosis and require presurgical chemotherapy following biopsy diagnosis. The tumor is thought to arise from a totipotential primitive stem cell, which can give rise to various elements and cell types. Surgical decisions, treatment, and prognostic categories depend on clinical factors (age and serum alpha fetoprotein levels), pretreatment imaging stage, pathologic stage, and histopathologic classification. Molecular testing currently has a minimal role in diagnosis and therapy, although it is important for research protocols.

II. Clinical factors and imaging

Recently, the Children's Hepatic Tumors International Collaboration (CHIC) identified the following factors as having the greatest prognostic significance for hepatoblastoma: PRETEXT imaging group, age, and serum alpha fetoprotein levels.[2] PRETEXT stands for pre-treatment extent of tumor and is now the most commonly used imaging staging system. The PRETEXT system assesses contiguous involvement of the four main liver segments and incorporates other factors including extrahepatic extension, involvement of other organs, distant metastases, and major vessel involvement. PRETEXT groups I through IV are assigned by determining the number of contiguous hepatic segments that would need resection in order to remove the entire tumor. For example, a PRETEXT group I tumor requires resection of only one segment, whereas a PRETEXT group III requires resection of three contiguous segments. PRETEXT groups I and II without major vascular involvement or metastases may be amenable to surgical resection prior to therapy.

III. Pathologic staging

The Children's Oncology Group (COG) staging system below is meant to be applied to tumors that are resected prior to treatment and requires both clinical information and pathologic features to accurately stage the tumor. It may offer additional important prognostic information to PRETEXT imaging. Biopsy prior to resection does not upstage the tumor.[3]

Stage I: Complete gross resection at diagnosis with clear margins

Stage II: Complete gross resection with microscopic residual at margins

Stage III: Unresectable tumor with biopsy only at diagnosis or gross total resection with nodal involvement, or tumor rupture or spill, or resection with gross residual

Stage IV: Distant metastatic disease at diagnosis

IV. Histopathologic subtypes

Hepatoblastomas can occasionally have only one component, but most have at least two or multiple components. Ninety percent of tumors are composed of two epithelial types, fetal and embryonal with or without other elements. The classification is based on epithelial type as listed below. The pure fetal epithelial type with low mitotic activity has the best prognosis, particularly when low stage and completely resected.[4] The small cell undifferentiated subtype is associated with a poor prognosis when associated with a rhabdoid phenotype and/or INI-1 loss. The significance of a small cell subtype without rhabdoid phenotype or INI-1 loss is less certain. In the current College of American Pathologists (CAP) tumor synoptic templates, all epithelial types present should be mentioned and the percentage of small cell undifferentiated component estimated, if present. Because the tumors are heterogeneous, they require extensive sampling. All nodules and grossly variant areas should be sampled. Histopathologic features are often altered by presurgical treatment. Response to

therapy and percent tumor necrosis following treatment may provide important prognostic and therapy-related information.

Hepatoblastoma Classification Modified From International Pediatric Liver Tumor Consensus Classification[5]

- Epithelial variants
  - Pure fetal with low mitotic activity (favorable histology, particularly in low-stage tumors)
  - Fetal, mitotically active
  - Pleomorphic, poorly differentiated
  - Embryonal
  - Small-cell undifferentiated (unfavorable histology)
    - INI1-negative (rhabdoid phenotype)
    - INI1-retained
  - Epithelial mixed (any/all above) Cholangioblastic
  - Epithelial macrotrabecular pattern
- Mixed epithelial and mesenchymal
  - With teratoid features (multiple heterologous and neuroectodermal components)
  - Without teratoid features (Figures 45-1 and 45-2)

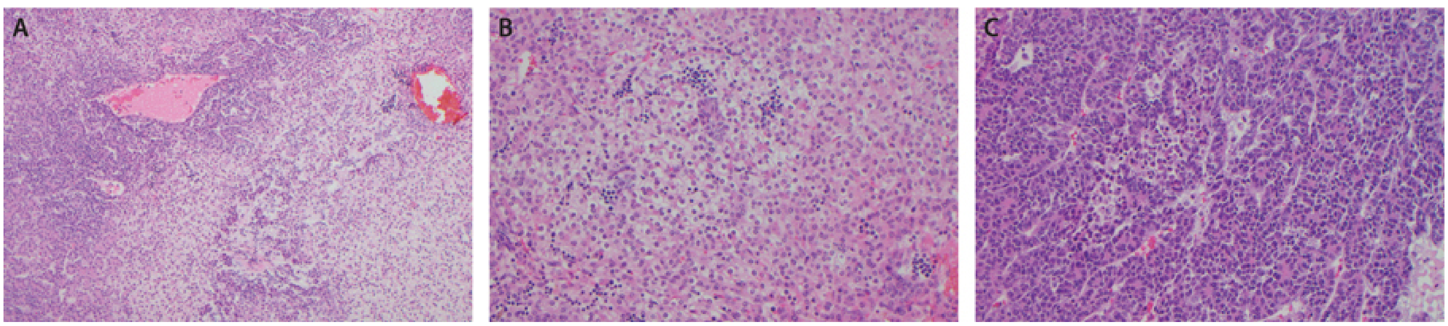

Figure 45-1. Histologic composite of hepatoblastoma. Mixed embryonal and fetal epithelial patterns (A), fetal component (B), embryonal component (C). Segmentectomy example 1.

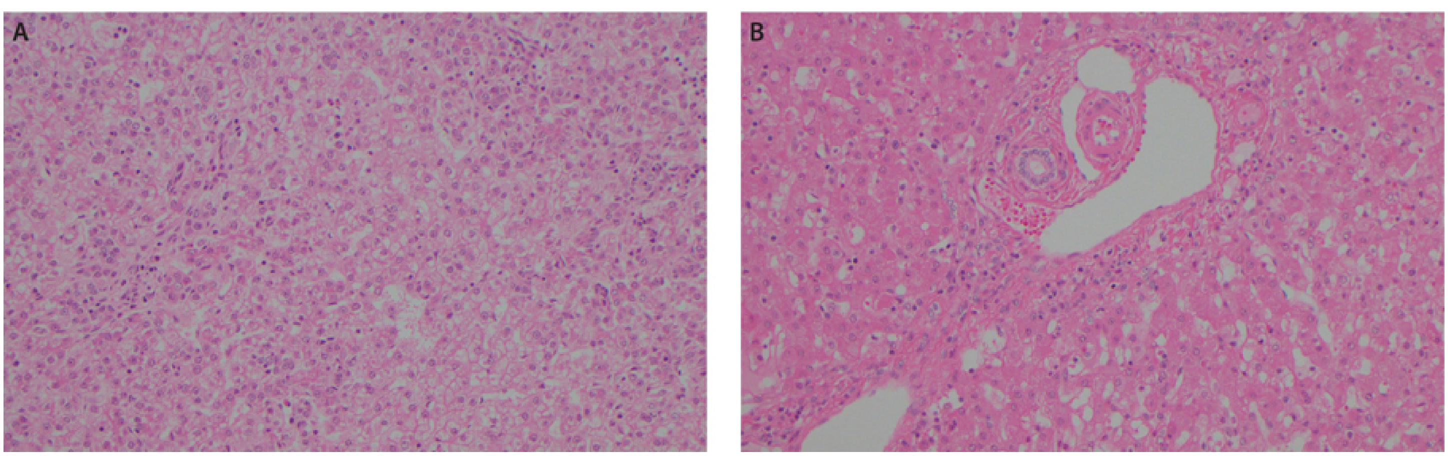

Figure 45-2. Pure fetal epithelial tumor with lo mitotic activity. Extramedullary hematopoiesis is present, and this example has abundant clear cytoplasm (A). Normal adjacent liver with portal tracts for comparison to tumor (B). Segmentectomy example 2.

V. Ancillary/molecular testing

Much tumor genetic sequencing and testing can now be done from formalin-fixed paraffin-embedded tissue, so freezing tissue or setting tissue aside for ancillary testing should be done only when ample tissue is available and will not compromise morphologic diagnosis.

Morphologic assessment is the main pathologic diagnostic modality in hepatoblastoma. Currently there are no definitive molecular or ancillary tests done in the routine clinical setting on these tumors. However, if ample tissue is received fresh, it is recommended to freeze tumor and normal liver tissue in case fresh-frozen tissue is needed. This tissue may be needed for treatment or clinical research protocols. In addition, if the tumor is not in fact hepatoblastoma, this tissue may be important for ancillary testing or clinical protocols. If enough tumor tissue is available, tissue can be placed in cell culture transport medium for tissue culture if standard cytogenetics or research protocol is needed.

VI. Specimen types[6,7]

Biopsy

Many tumors present late stage or are unresectable prior to therapy. In these cases, needle biopsy or open biopsy specimens may be sent for diagnosis prior to therapy. Histologic assessment is the priority for diagnosis, and most or all of the tissue should be submitted for histologic diagnosis. Five to 10 core needle biopsies measuring 1 cm to 2 cm in length and 1 mm in diameter taken from multiple areas of the tumor should be adequate sampling. A single open biopsy should contain at least 1 cm^3 of tumor. It is a good idea to send the tissue fresh to pathology for assessment of tumor viability and specimen adequacy. Touch preparations or frozen section can be done for this purpose. This also allows for triage of the tissue in case another type of tumor is suggested. If ample biopsy tissue is received, portions can be reserved frozen for possible ancillary studies, and tumor may be sent fresh in tissue culture medium for cytogenetics. However, this should not be done if tissue is limited as morphologic diagnosis is the most important modality in hepatoblastoma diagnosis.

Segmentectomy or partial hepatectomy example 1

These gross photographs (Figure 45-3A-C) are from the same partial hepatectomy specimen weighing 212 g and containing an 8.5-cm hepatoblastoma in the left lobe of the liver. The resected surface is inked (black arrow) and located 2.5 cm from the tumor, which has a slightly infiltrative border. The tumor is heterogeneous with white fleshy areas alternating with hemorrhagic areas. The tumor bulges against the liver capsule (red arrows) but does not penetrate the capsule. Microscopically wisps of capsule, less than 1 mm thick surrounded the tumor and margins were negative. This tumor was 95% epithelial with equal components of fetal and embryonal patterns (see Figure 45-1A-C). Five percent of the tumor was mesenchymal including osteoid. It is important to weigh the specimen, ink the specimen surfaces, note the distance of the specimen from the resection margin, sample the resection margin, and liberally sample the capsular surface over the tumor. In this case, sections should include nine of tumor and one of normal liver. One-gram aliquots of fresh tumor and normal liver should be frozen for future ancillary studies. This tumor was resected prior to treatment and would qualify as COG stage I.

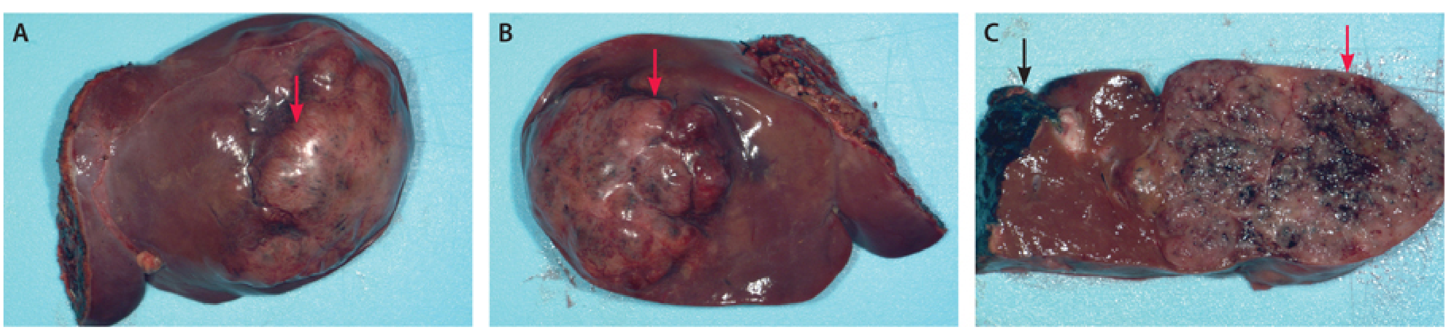

Figure 45-3. Superior (A), inferior (B), and cut surfaces (C) of the partial hepatectomy. Segmentectomy example 1.

Segmentectomy example 2

Segmentectomy specimen of liver with 11-cm untreated tumor is illustrated in Figure 45-4. The specimen weighed 440 g. The tumor is well circumscribed with a thin pseudocapsule (blue arrow) and thin rim of liver parenchyma (black arrow) surrounding the tumor. Margins were negative. Grossly, the tumor is homogeneous

and yellow, and this correlates microscopically with a pure epithelial variant with high clear cell content, which was 100% pure fetal pattern with low mitotic activity (see Figure 45-2). This tumor would have an excellent prognosis. It is COG stage I and has favorable histology. It is important to weigh the specimen, ink the surface, record the closest gross margin, and submit at least 11 sections of tumor to include sampling of the closest margins. Sections should also include one with as much normal liver as possible. One-gram aliquots of tumor and of normal liver should be frozen for possible future ancillary studies.

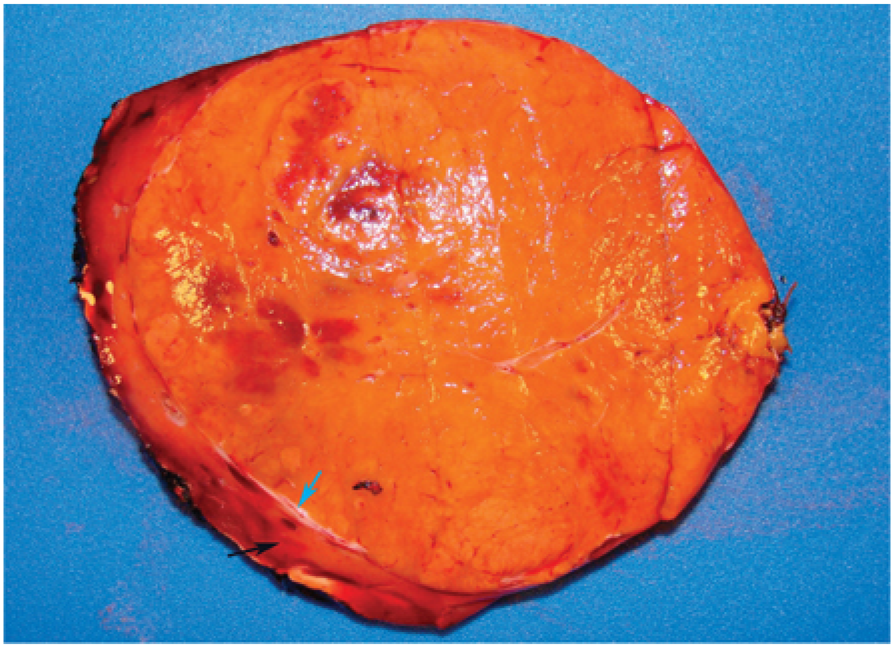

Figure 45-4. Cut surface of pure fetal epithelial tumor. Segmentectomy example 2.

Hepatectomy example 3

Hepatectomy specimen with treated tumor is illustrated in Figure 45-5. The specimen measures 22 cm in maximum dimension and weights 990 g. This was a PRETEXT IV hepatoblastoma diagnosed on biopsy. PRETEXT imaging showed most tumor in the left lobe with diffuse, multinodular involvement throughout the liver with major involvement of the portal vein and no extrahepatic extension or metastases. Vascular margins are tied in the portal region and are uninvolved. The treated tumor was 60% viable, with most of the tumor located in the left lobe. There was also prominent vascular invasion and spread throughout the liver. Tumor did not extend through the capsular surface. The specimen was weighed and inked prior to coronal sectioning. En face vascular margins from the portal area and an en face margin of the porta hepatis fibrous tissue were obtained as were numerous sections showing relationship of tumor to the liver capsule. A tumor map was generated to estimate percent tumor necrosis. Red arrow – ligated vascular margins at porta hepatis. Black arrows – tumor underneath liver capsule.

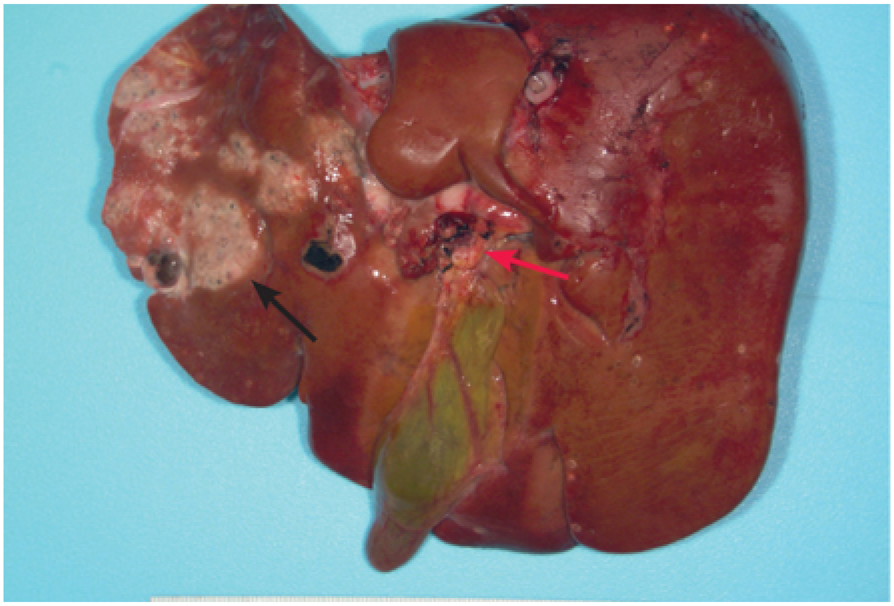

Figure 45-5. Liver explant after treatment. Hepatectomy example 1.

Hepatectomy example 4

This hepatectomy specimen (Figure 45-6) was received posttreatment. It was coronally sectioned keeping left and right lobes intact and showing location of tumor and relationship to capsule and porta hepatis. Imaging was PRETEXT IV involving all liver segments without extrahepatic spread, major vascular involvement, or distant metastases. The specimen weighed 375 g and the residual tumor measured 8.5 cm in maximum dimension. The histology was approximately 90% fetal pattern and 9% embryonal pattern with focal minimal mesenchymal component, 1%. Tumor sampling included at least nine tumor sections. These sections included relationship to capsule. En face vascular and porta hepatis bile duct margins were submitted. A tumor map of one cross-section (Figure 45-7) was used to assess tumor necrosis. One section of normal liver was submitted. Four hepatic artery lymph nodes were received as a separate specimen and were completely submitted.

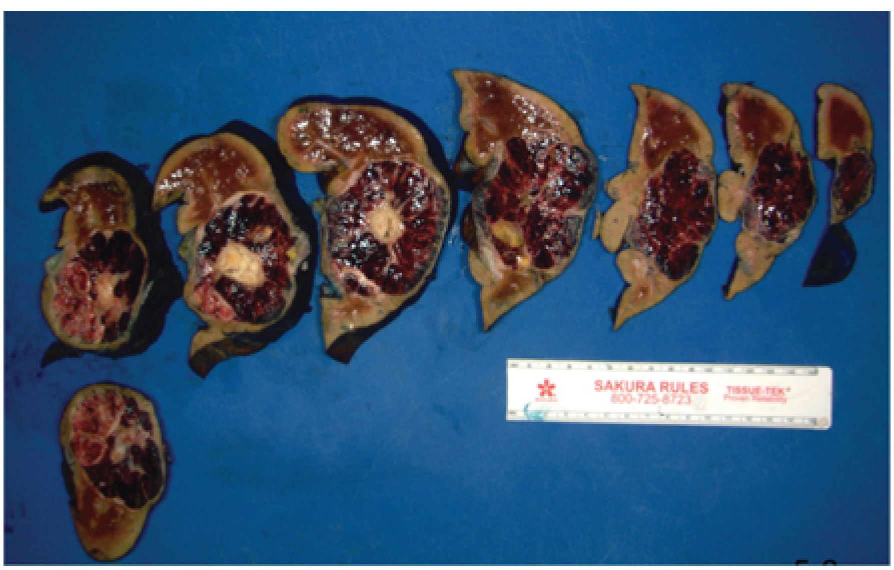

Figure 45-6. Series of bread-loaf cuts of explant liver with tumor. Hepatectomy example 2.

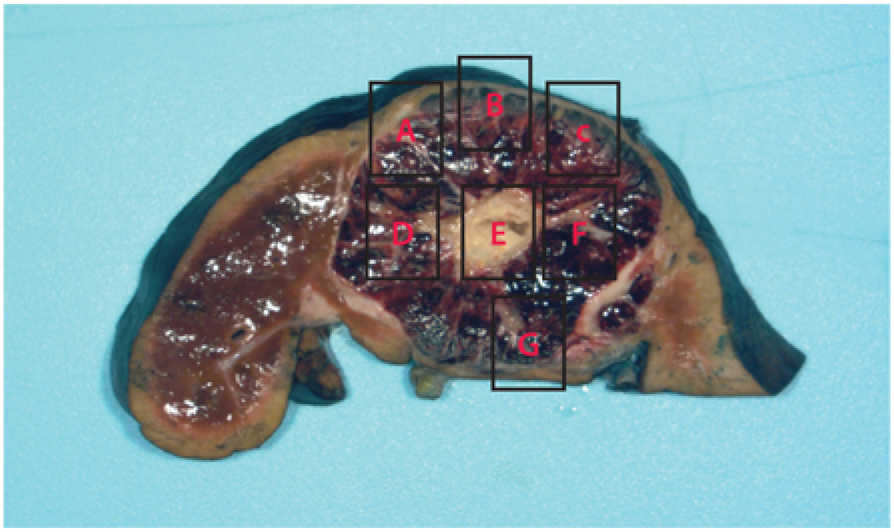

Figure 45-7. Mapping of the tumor after treatment.

VII. Grossing instructions

Partial hepatectomy or total hepatectomy specimens should be received fresh.

1. Orient, weigh and photograph the specimen.
2. Determine location of the tumor relative to right or left lobe.
3. Examine the resection margin, capsular surface, and porta hepatis for any sutures or vessels or orientation by the surgeon.
4. Examine the porta hepatitis and take vascular and bile duct en face margins prior to inking. Porta hepatis fibrous tissue can also be submitted as an en face margin if vessels and ducts are not grossly identified.
5. Examine the gallbladder and caudate lobe.
6. Note any areas where the tumor is beneath or possibly through the liver capsule, and be sure to sample these areas.
7. Ink the specimen prior to sectioning.
8. Make cross-sections 1 cm to 2 cm thick through the specimen. The cross-sections can be coronal, which keeps the right and left lobes together and helps to locate the tumor. Alternatively they can be sagittal right to left along the long axis of the liver. The important point is to show relationship of the tumor to the inked surfaces including porta hepatis and capsular surfaces.
9. Identify the tumor and determine location and if unifocal or multifocal. Take fresh aliquots of normal liver and of all tumor nodules. This tissue should be stored frozen at -80°C.
10. The tumors can be very soft, so fixation overnight after initial sectioning may be necessary.
11. All separate tumor nodules should be sampled as should varying areas. Take one section of tumor per maximum tumor dimension. For example, 10 sections of tumor should be submitted if the maximum tumor dimension is 9 cm to 10 cm.
12. Tumor sections are best taken to demonstrate relationship to margins, vessels, and porta hepatis.
13. A tumor map of a cross-section can be made to document posttreatment necrosis, multiple tumor nodules, and relationship of tumor to margins

Example gross description

Specimen 1: Received fresh in a container labeled with the patient name and medical record number, and designated “native liver,” is a hepatectomy specimen that weighs 375 g. The liver is minimally distorted and measures 13.6 cm laterally, 9.1 cm anterior to posterior, and 6.5 cm superior to inferior. The inferior surface has a well-defined caudate lobe and intact and smooth gallbladder, neither of which is involved by tumor. The porta hepatis is free of tumor. Ligated vessels and bile duct are free of tumor. The capsular surface is smooth and without tumor penetration, but tumor bulges against the central superior and anterior surfaces. The external surface of the specimen is inked black. Coronal cross-sections along a superior to inferior plane contain a

single, irregular, well-demarcated tumor occupying the central portion of the liver and extending into the right and left liver lobes, with tumor replacing 75% of the liver. Tumor dimensions are 8.5 x 6.7 x 6.0 cm. The tumor has a pushing border and is dark purple and soft with focal white fibrous areas. The tumor pushes against the capsular surface in multiple areas with a gross margin of less than 1 mm in multiple areas. The tumor comes to within 0.5 cm of the porta hepatis. No gross vascular invasion or extrahepatic extension is identified. The uninvolved liver is red-brown without fibrosis or satellite tumor nodules. A representative portion of tumor is stored frozen. A representative portion of uninvolved liver is stored frozen. Section code follows:

1A-1G: Sections of tumor to include entire cross-section of tumor

1A-1C: Include closest capsular margins (black ink on surface)

1G: Includes tumor closest to porta hepatis

1H: Additional two representative sections of liver with closest capsular surfaces

1I: Uninvolved liver adjacent to tumor

IJ: Vascular en face margin, porta hepatis en face margin, and bile duct en face margin

1L: Gallbladder and section from caudate lobe

Specimen 2: Received fresh in a container labeled with the patient name and medical record number and designated hepatic artery lymph nodes is a piece of soft fibroconnective tissue with possible lymph nodes. The tissue measures 0.5 x 0.4 x 0.3 cm. It is entirely submitted in a single cassette.

VIII. Sample final pathology report

1. Native liver, hepatectomy:

Hepatoblastoma, status post treatment

Mixed epithelial and mesenchymal subtype

- 45% fetal well-differentiated mitotically inactive
- 45% fetal mitotically active
- 9% embryonal
- 1% mesenchymal

Tumor size 8.5 cm with complete resection

Vascular and bile duct margins negative for tumor

Tumor within 1 mm of capsular surface

No lymphvascular invasion

Tumor necrosis 40%

2. Hepatic artery lymph nodes, biopsy:

Four lymph nodes negative for tumor

Synoptic report

Explanted Liver

Tumor size 8.5 x 6.7 x 6.5cm

Unifocal

Tumor confined to liver

Preoperative therapy given

Histologic Types Present:

- Hepatoblastoma, epithelial type fetal pattern mitotically inactive
- Hepatoblastoma, epithelial type fetal pattern mitotically active
- Hepatoblastoma, epithelial type, embryonal
- Hepatoblastoma, mesenchymal type, without teratoid features

Treatment Effect: Present, 40% tumor necrosis

Margins:

- Porta hepatitis, vascular, bile duct margins and capsule uninvolved by tumor
- Closest margin – capsular surface, less than 1 mm to margin

Macroscopic lymphvascular invasion not identified

Microscopic lymphvascular invasion not identified
Regional lymph nodes: 4 hepatic artery lymph nodes negative for tumor
COG stage not given due to presurgical treatment
Additional findings in background liver: none
Serum alpha fetoprotein level: not known
Ancillary studies –none

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6. Rudzinski E, Ranganathan S, Hicks J, Kim G. Protocol for the Examination of Resection Specimens From Patients With Hepatoblastoma. February 2019. College of American Pathologists. Available at www.cap.org/cancerprotocols.
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46. Neuroblastoma

Hong Yin, MD; Heather Rytting, MD; Shelley Caltharp, MD; Beverly Rogers, MD

Background

Neuroblastoma is the most common extracranial solid tumor in children, originating from neural crest cells during early sympathetic neurogenesis. The abdomen is the most common site of neuroblastoma, with the majority arising in the adrenal glands and much less commonly in the paravertebral sympathetic chains. The second most common primary site is posterior mediastinum.

Treatment for neuroblastoma varies based on the risk for relapse classification of the disease. For children with low-risk disease, surgical removal of the tumor may be all that is necessary. For patients with intermediate risk of relapse, chemotherapy is given initially to shrink the tumor and make it easier for the surgeon to remove. High-risk patients require treatment with multimodal therapy using chemotherapy, surgery, radiotherapy, stem cell transplant, biologic agents, and immunotherapy.[1]

Histopathologic classification

1. Neuroblastoma (Schwannian stroma-poor): Schwannian stroma comprising <50% of the tumor

- Undifferentiated neuroblastoma (small blue round cell tumor) (Figure 46-1)
- Poorly differentiated neuroblastoma (neuropil identified, <5% maturing/mature ganglion cells) (Figures 46-2 through 46-4)
- Differentiating neuroblastoma (>5% maturing/mature ganglion cells) (Figures 46-5 and 46-6)

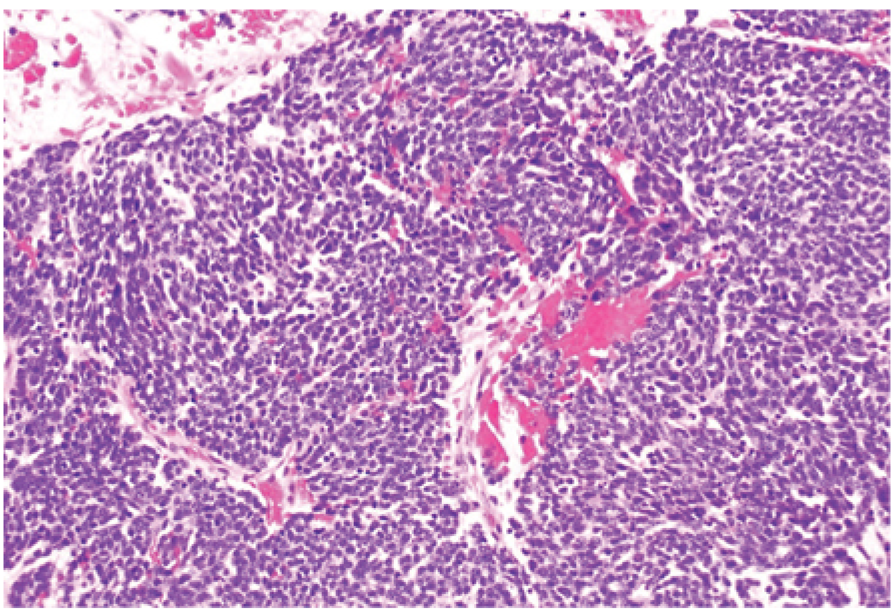

Figure 46-1. Undifferentiated neuroblastoma is composed of a uniform population of small blue round cells and can be focally spindled without neuropil or rosettes. The tumor cells are arranged in sheets or lobules separated by thin fibrovascular septa. The tumor cells have round to ovoid nuclei with salt-and-pepper chromatin, high nuclear:cytoplasmic ratio, scanty cytoplasm, and ill-defined cytoplasmic borders, and sometimes contain distinct nucleoli. They are positive for vimentin. This histology is often associated with a high mitosis-karyorrhexis index (MKI) and *MYCN* amplification.

Figure 46-2. Schwannian stroma-poor, poorly differentiated neuroblastoma. A well-circumscribed solid mass with a gray-white fresh soft cut surface and hemorrhagic dark red areas.

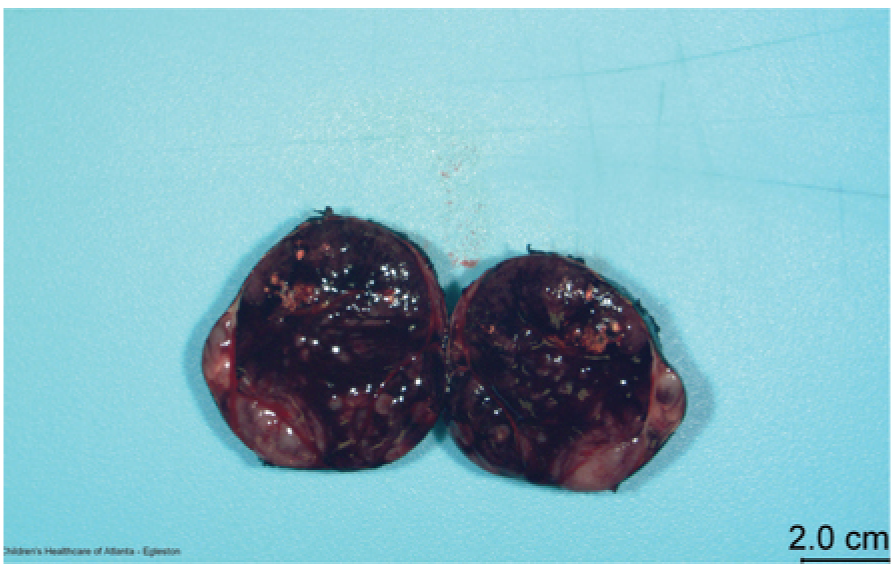

Figure 46-3. Schwannian stroma-poor, poorly differentiated neuroblastoma. A well-circumscribed solid mass with a hemorrhagic dark red soft cut surface and punctate white calcifications.

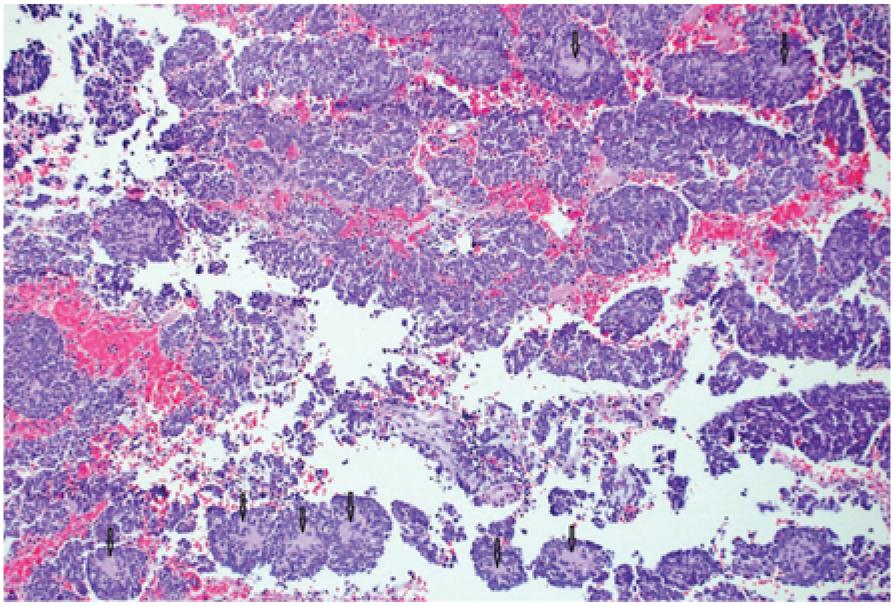

Figure 46-4. Schwannian stroma-poor, poorly-differentiated neuroblastoma is composed of neuroblasts with high nuclear:cytoplasmic ratio and less than 5% the tumor showing ganglion cell differentiation. The tumor shows Homer-Wright rosettes consisting of an arrangement of tumor cells around a central area filled with neuropil (neurofibrillary processes, black arrows). The background is hemorrhagic.

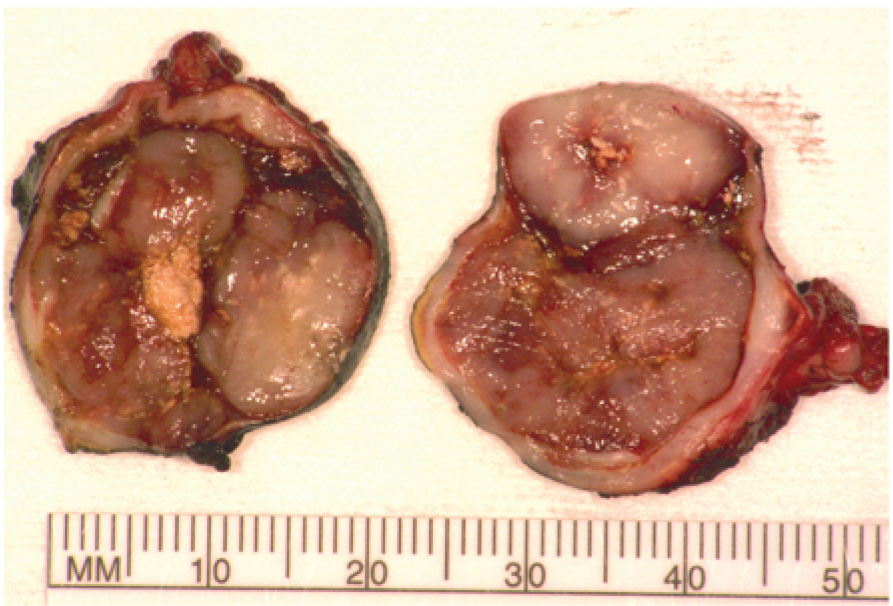

Figure 46-5. Schwannian stroma-poor, differentiating subtype of neuroblastomas. A well-circumscribed solid mass with a multinodular, grayish-white to pink-tan, soft fleshy cut surface and punctuated coarse calcifications.

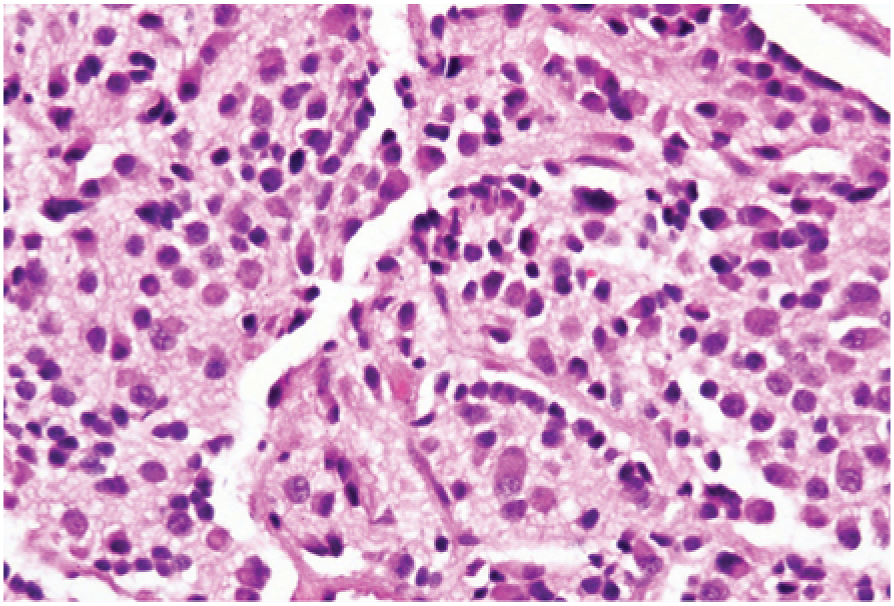

Figure 46-6. Differentiating neuroblastomas have abundant neuropils, and >5% of tumor cells show differentiation toward ganglion cells. Differentiating neuroblasts have moderate to abundant acidophilic or amphophilic cytoplasm and an enlarged eccentric vesicular nucleus, sometimes with a single prominent nucleolus.

2. Ganglioneuroblastoma: >50% Schwannian stroma

- Nodular ganglioneuroblastoma (composite, two or more Schwannian stroma-rich/dominant and stroma-poor nodules) (Figures 46-7 thriough 46-10)
- Intermixed ganglioneuroblastoma (Schwannian stroma-rich) (Figure 46-1)

Figure 46-7. Ganglioneuroblastoma, nodular subtype. A well-circumscribed 2 x 2 x 2 cm dark-red hemorrhagic poorly differentiated neuroblastoma soft nodule is within a tan-white firm 4 x 3 x 2 cm ganglioneuroma. Nodular ganglioneuroblastomas are composite tumors and, in general, have grossly visible nodules of poorly differentiated hemorrhagic tumor. It is important to document and sample each nodule. If possible, freeze tissue from each nodule for molecular testing since each nodule represents a different tumor clone. In these tumors, the most unfavorable subtype found will determine classification as favorable or unfavorable.

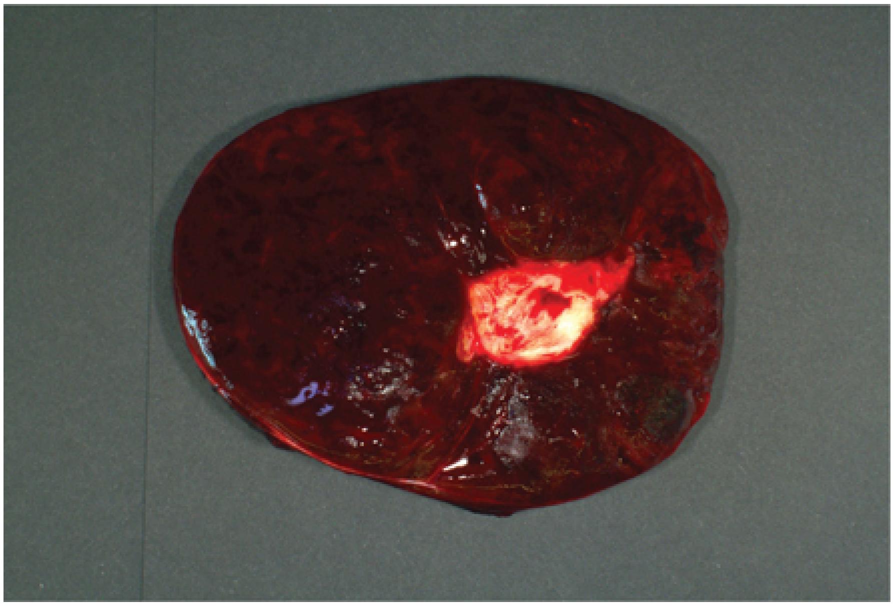

Figure 46-8. Ganglioneuroblastoma; nodular subtype with predominantly poorly differentiated neuroblastoma. The poorly differentiated neuroblastoma measures 15.5 cm with a dark-red hemorrhagic soft cut surface. In the center is a well-circumscribed, tan-white, firm, 4 x 2.5 x 2 cm ganglioneuroma component. Sample both areas and reserve tissue from each area for separate ancillary and molecular testing if necessary.

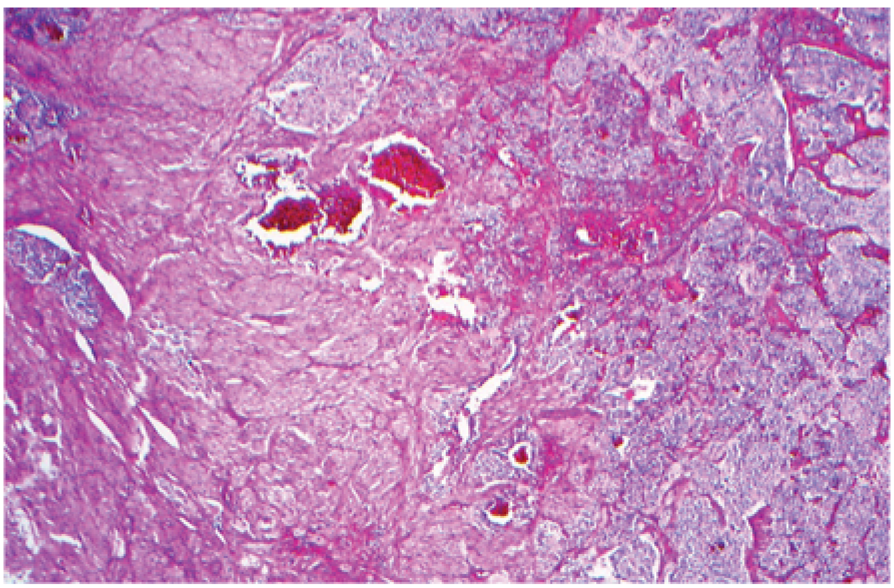

Figure 46-9. Ganglioneuroblastoma, nodular subtype: Demarcation between Schwannian stroma-dominant mature ganglioneuroma (left) and Schwannian stroma-poor neuroblastoma (right).

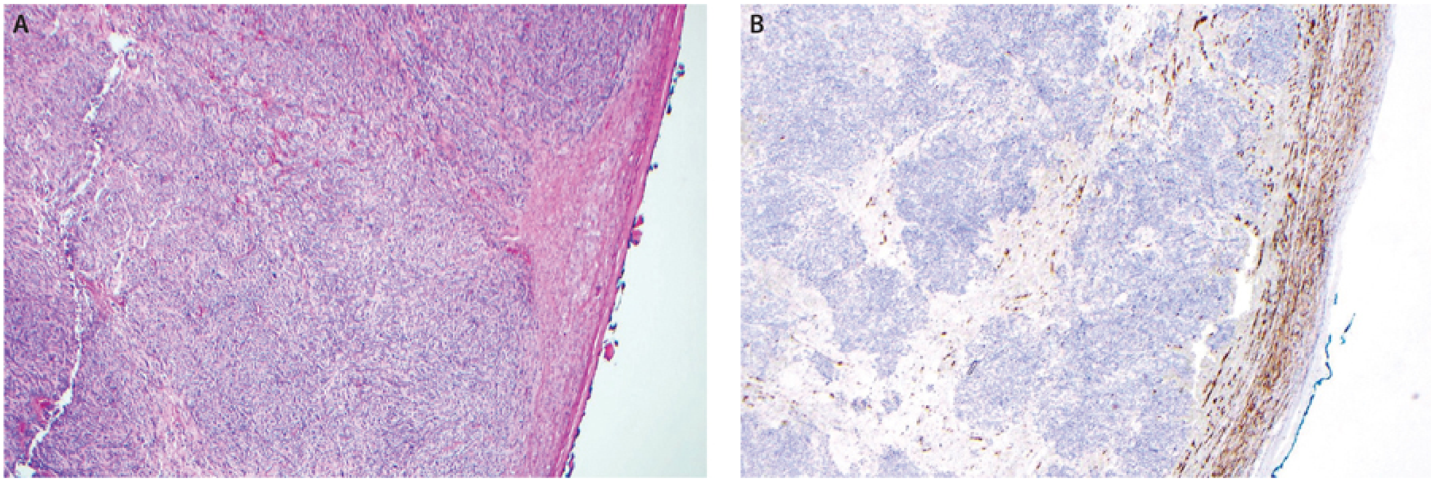

Figure 46-10. A. Ganglioneuroblastoma, nodular subtype: Demarcation between Schwannian stroma-poor, poorly-differentiated neuroblastoma (right) and a ring of Schwannian stroma-dominant mature ganglioneuroma (left). Careful examination of gross specimen and multiple sections from capsule are important to identify the ganglioneuroma rim and classify the tumor as nodular subtype of ganglioneuroblastoma. It is likely that a malignant clone arose in a mature tumor and replaced most of the tumor, leaving only a small rim of mature tumor. B. S100 stain highlights the Schwannian stroma in the residual rim of ganglioneuroma.

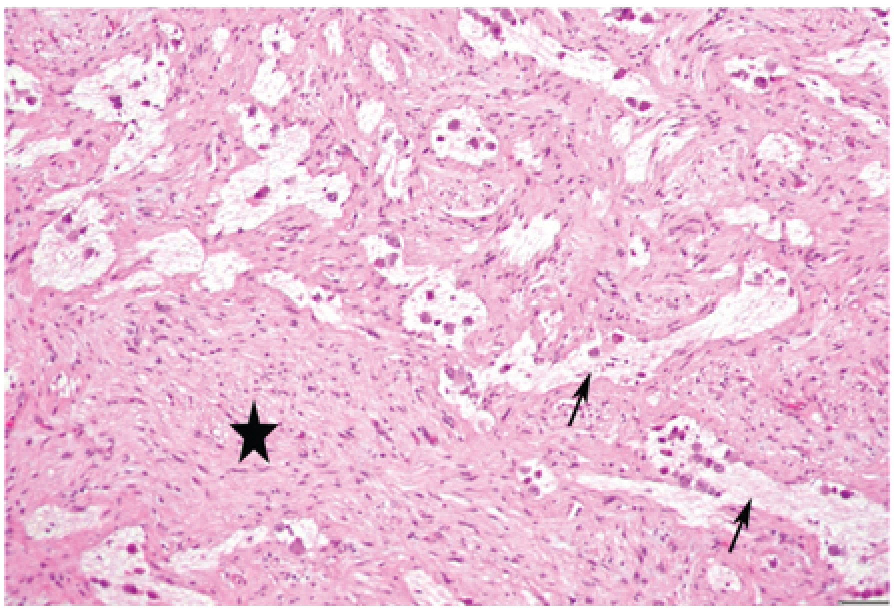

Figure 46-11. Schwannian stroma-rich (>50%), intermixed ganglioneuroblastoma. Well-delineated nests of maturing neuroblasts are scattered throughout and are associated with a light loose background of neuropil (arrows). Fully mature tumors will not have neuropil. This tumor will be white-yellow and firm, and indistinguishable grossly from a ganglioneuroma. The star designates the Schwannian stroma.

3. Ganglioneuroma: Schwannian stroma-dominant, no islands of neuropil
   - Maturing ganglioneuroma (Figure 46-12)
   - Mature ganglioneuroma

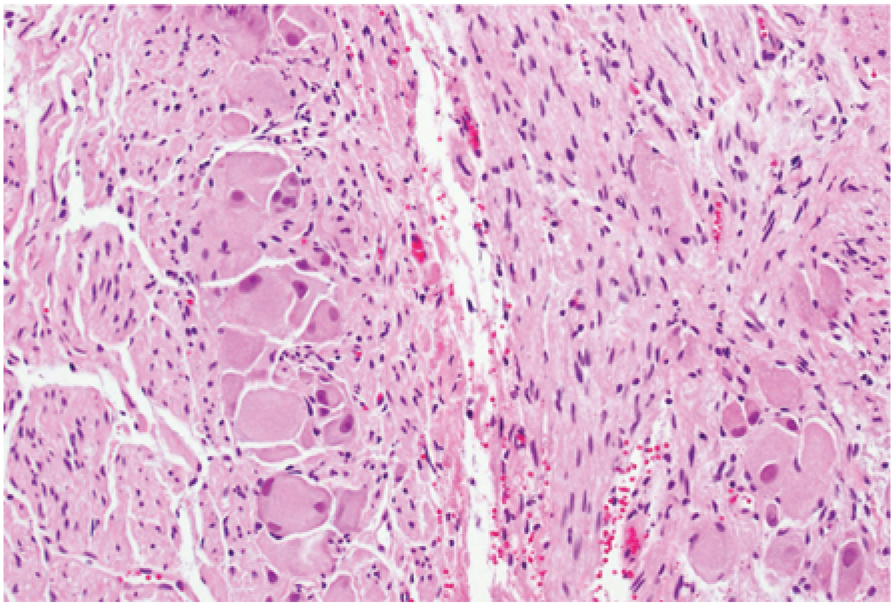

Figure 46-12. Ganglioneuroma, maturing subtype: Schwannian stroma is predominant with minor, scattered groups of differentiating neuroblasts or maturing ganglion cells admixed with completely mature ganglion cells. There are no islands of neuropil.

4. Neuroblastic tumor, unclassifiable

International Neuroblastoma Pathology Classification (INPC)[2,3]

1. Favorable histopathology
   A. Neuroblastoma (Schwannian stroma-poor)
   - Poorly differentiated subtype, low or intermediate mitosis-karyorrhexis index (MKI), <18 months old
   - Differentiating subtype, intermediate MKI, <18 months old
   - Differentiating subtype, low MKI, <5 years old

   B. Ganglioneuroblastoma, nodular (list least favorable nodule)
   - Poorly differentiated subtype, low or intermediate MKI, <18 months old
   - Differentiating subtype, intermediate MKI, <18 months old
   - Differentiating subtype, low MKI, <5 years old

   C. Ganglioneuroblastoma, intermixed (Schwannian stroma-dominant), any age

   D. Ganglioneuroma (Schwannian stroma-dominant), mature or maturing, any age
2. Unfavorable histopathology
   A. Neuroblastoma (Schwannian stroma-poor)
   - Undifferentiated subtype, any MKI, any age
   - Poorly differentiated subtype, high MKI, any age
   - Poorly differentiated subtype, low or intermediate MKI, >18 months old
   - Differentiating subtype, high MKI, any age
   - Differentiating subtype, intermediate MKI, >18 months old
   - Differentiating subtype, low MKI, >5 years old

   B. Ganglioneuroblastoma, nodular (list least favorable nodule)
   - Undifferentiated subtype, any MKI, any age
   - Poorly differentiated subtype, high MKI, any age
   - Poorly differentiated subtype, low or intermediate MKI, >18 months old
   - Differentiating subtype, high MKI, any age
   - Differentiating subtype, intermediate MKI, >18 months old
   - Differentiating subtype, low MKI, >5 years old
3. Not applicable secondary to previous chemotherapy

4. Cannot be determined secondary to insufficient material

Staging

There are two staging systems for neuroblastoma: International Neuroblastoma Staging System[4] (INSS) and International Neuroblastoma Risk Group Staging System (INRGSS). Pathologists are not required to report neuroblastoma staging for the College of American Pathologists (CAP) protocol template.

International Neuroblastoma Staging System (INSS)

This staging system is for postoperative patients and mainly for prognosis.

Stage 1 (Figure 46-13)

- Localized tumor with complete gross excision with or without microscopic residual disease
- Contralateral and representative ipsilateral regional lymph nodes negative for disease (nodes attached to and removed with primary tumor may be positive)

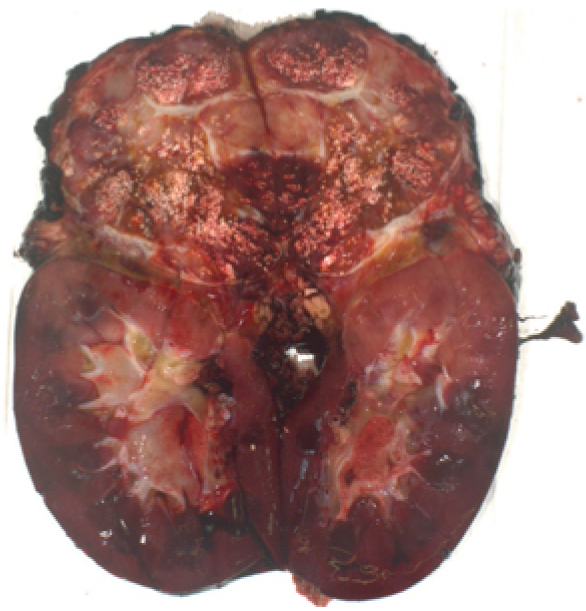

Figure 46-13. This is the typical location of a neuroblastoma: above the upper pole of the kidney. The tumor was previously diagnosed poorly differentiated neuroblastoma, status postchemotherapy effects: approximately 30% necrosis and calcification of the suprarenal mass. The tumor does not invade the kidney parenchyma and completely grossly excised, stage I.

Stage 2A

- Localized tumor with incomplete gross excision
- Ipsilateral and contralateral nodes negative for tumor

Stage 2B

- Localized tumor with complete or incomplete resection
- Positive ipsilateral (nonadherent) nodes
- Contralateral nodes negative for tumor

Stage 3 (Figure 46-14)

- Unresectable unilateral tumor that crosses the midline with or without regional lymph node involvement or
- Localized tumor with contralateral regional lymph node involvement or
- Midline tumor with bilateral extension by infiltration or by lymph node involvement

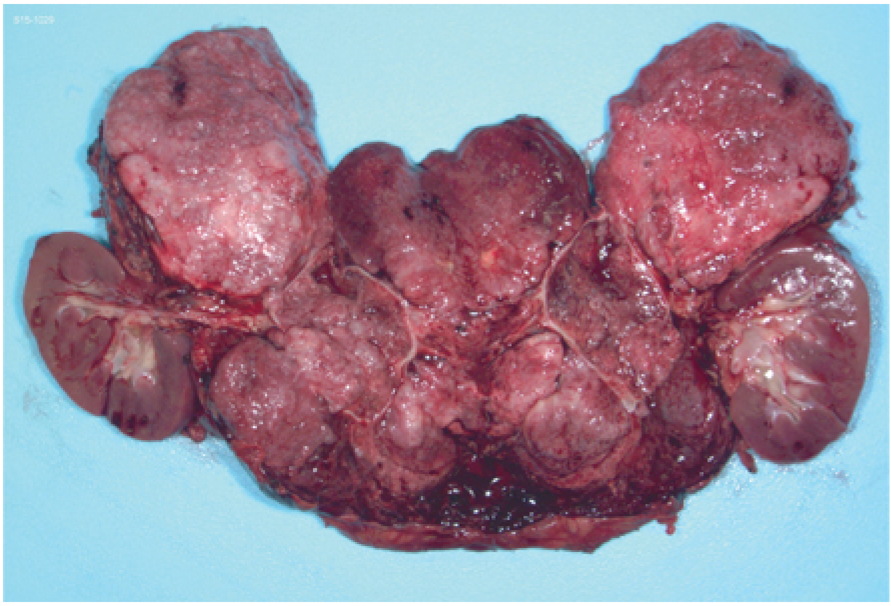

Figure 46-14. Bulky tumor that crosses the midline (pretreatment), stage 3.

Stage 4
- Distant metastases not fulfilling stage 4S

Stage 4S
- <1 year of age
- Localized tumor (stage 1, 2A, or 2B) distant metastases confined to skin, liver, and/or bone marrow
- Marrow involvement should be minimal (less than 10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). A meta-iodobenzylguanide (MIBG) scan if performed should be negative for disease in the bone marrow.

International Neuroblastoma Risk Group Staging System (INRGSS)

INRGSS uses only the results of imaging tests taken before surgery. Knowledge regarding the presence or absence of image-defined risk factors (IDRF) is required for this staging system.

Stage L1
- Localized tumor confined to one body cavity and not involving imaged-defined risk factors (IDRFs)

Stage L2
- Regional tumor involving one or more IDRFs

Stage M
- Distant metastases (excludes metastases to local lymph node, except stage MS)

Stage MS
- Metastases in patients <18 months, confined to skin, liver, and/or bone marrow (less than 10% bone marrow involvement)

Neuroblastoma resection specimen type and gross techniques

Tumors should be received fresh. They may be pre or post treatment. This is important to note because histopathologic classification is accurate only on nontreated tumors since treatment-related maturation is common. Grossing techniques can affect histologic classification and staging of the tumor and impact patient treatment. Ploidy, *N-Myc* amplification, and loss of heterozygosity have been used as genetic markers for risk stratification and therapeutic decision-making. Fresh tissue may be required for these special studies, depending on the methodology employed. Amplification of the *N-Myc* oncogene (near-diploidy or tetraploidy), loss of heterozygosity of 1p, 11q, 14q, and *ALK* mutation as well as amplification correlate with a worse prognosis and aggressive disease. Hyperdiploidy and increased TrkA (high-affinity nerve growth factor receptor) expression associate with better prognosis.[5]

Resection of the primary tumor of stage I or II disease or biopsy is performed to collect tissue samples for biologic studies used to assign the patient into the appropriate risk category. Most centers in the United States perform limited open biopsies when the primary tumor is unresectable upfront. Adequate tissue is needed to perform molecular studies that aid in risk assignment. Ideally, the specimen should be received fresh and unfixed to allow the pathologist a full range of biologic studies options.

Submission of tissue, priority as follows:

1. Formalin-fixed tissue for morphologic evaluation.
2. Frozen aliquots for ancillary/molecular testing. Aliquots of tumor from each tumor nodule are needed.
3. Ten touch preparations from fresh tumor can be prepared for molecular testing/FISH analysis. If touch preparations are made, they should be air dried and stored at -20°C.
4. A 0.5 x 0.5 x 0.5 cm aliquot of tissue may be set aside for flow cytometry ploidy study.
5. Additional tumor may be frozen at -80°C and stored in tumor bank for future studies.

Most ancillary studies are done from formalin-fixed paraffin-embedded tissue sections and frozen tissue, so 1-2 above are the most important.

Surgical specimen type includes simple resection of nonadrenal tumor (usually not oriented), adrenalectomy, and radical nephrectomy with adrenalectomy.

1. Orient the specimen; look for any orientation provided by the surgeon.
2. Weigh the specimen and document any surfaces involved by tumor.
3. Submit en face margins of artery and vein, often ligated.
4. Ink surgical resection margins one color and serosal surface another color.
5. Serially section the specimen in the longest dimension. Describe the texture of the lesion. The firm and white areas could be mature Schwannian stromal component. Look for any fibrous rim of Schwannian component. Look for any hemorrhagic or cellular appearing nodules within firm and white Schwannian stroma.
6. Make 10 touch preparations.
7. Snap freeze tumor tissue, store at -80°C.
7. After prepping specimen, fix serial sections overnight.
8. Take sections from central and peripheral areas of the tumor according to common guidelines (at least one tumor section per centimeter) and surgical margins.
9. All distinct nodules or hemorrhagic foci should be individually sampled. A photograph and tumor section map can help correlate pathologic findings with each nodule.

The gross features may correlate with the histologic subtype and secondary treatment changes. They are important to document and sample. and include dark-red hemorrhage, yellow-white necrosis, and coarse or fine calcifications (Figure 46-15). Undifferentiated and poorly differentiated areas are tan-white to gray, fleshy and soft, and often can be dark-red and hemorrhagic.

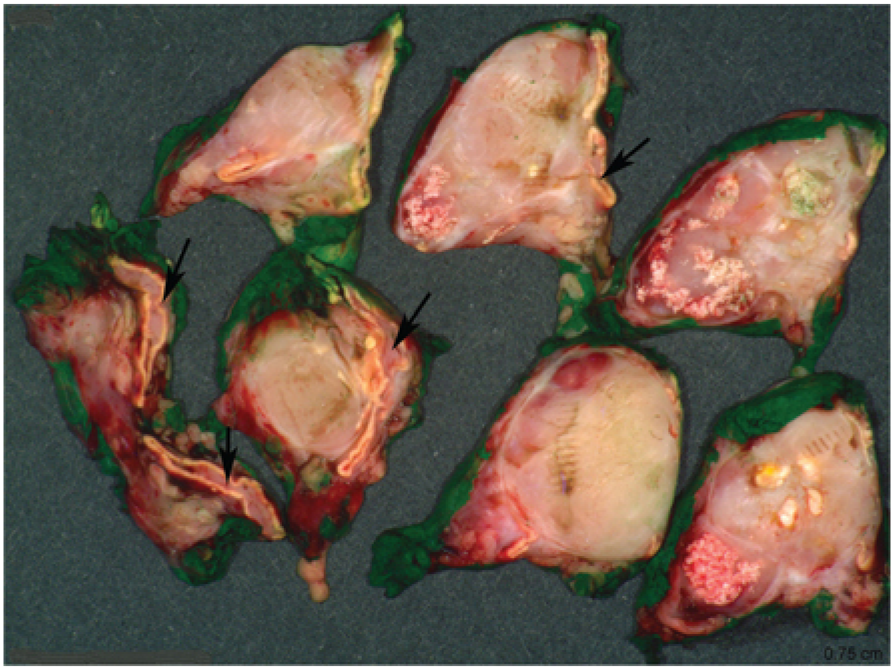

Figure 46-15. This is a treated tumor that was previously diagnosed undifferentiated neuroblastoma, unfavorable histology. Posttherapy effects include 40% viable neuroblastoma, 30% viable tumor with ganglion cell differentiation, and 30% necrotic tumor with calcifications. This tumor arose in the adrenal and is surrounded partially by a thin bright-yellow rim of adrenal cortex (black arrow). The cut surface is tan-white with abundant coarse, punctate, white calcifications and yellow-white soft necrosis. The tumor is present at inked surgical margin.

Example report (Figure 46-14)

Gross description

Specimen A is received fresh in a container labeled with the patient name, medical record number, and "retroperitoneal neuroblastoma." The specimen measures 18.0 x 17.0 x 7.0 cm and weighs 629 g. There is a left kidney attached that measures 8.5 x 4.4 x 4.2 cm. The mass is multiloculated with a capsule and is inked in black. The tumor encases the renal vasculature. Renal vessels and ureter are ligated with black sutures and are free of tumor involvement. The ureter measures 0.8 cm in length, 0.2 cm in diameter. Adrenal gland is not identified. The specimen is bivalved through the kidney and ureter, and multiple serial sections are examined. The cut surfaces of the tumor are multinodular, gray-white to pink-tan, and soft. Dark-red hemorrhagic areas measure less than 0.5 cm in diameter and are dispersed throughout the tumor. There is no firm white stroma to suggest a composite tumor. No necrosis is seen. The tumor does not invade the renal capsule and parenchyma. The renal cortex measures 0.3 cm thick. No nodules or cysts are identified. Calyx, pelvis, and ureter are not dilatated or narrowed. Three possible lymph nodes are identified in the hilar area and range in size from 0.6 cm to 1.0 cm. Ten touch preparations are made from the tumor. Two portions of fresh kidney and two portions of fresh tumor are frozen and stored at -80°C for ancillary studies and tumor banking. Representative sections are submitted as follows:

A1: En face margins of renal artery, vein, and ureter
A2: Kidney closest to tumor
A3: Kidney away from tumor
A4-A5: Thickened tumor capsule and tumor
A6-A7: Closest resection margins and tumor
A8-A9: Possible adrenal grand and tumor
A10-A13: Reprehensive sections of tumor
A14-A15: Hemorrhagic areas
A16: Three lymph node candidates

Diagnosis

Right Kidney, Radical Nephrectomy with Adrenalectomy:
- Previous stroma-poor, poorly differentiated neuroblastoma with posttreatment maturation
- Specimen weighing 629 gm, measuring 18 cm
- Less than 10% tumor necrosis
- Tumor encases the renal artery
- No adrenal gland identified
- No lymphvascular invasion identified
- Surgical resection margins negative for tumor
- Three reactive lymph nodes negative for tumor (0/3)
- Kidney with no pathologic diagnostic abnormality
- See synoptic report

Neuroblastoma resection synoptic report

Specimen: Other (specify): right kidney
Procedure: Resection Radical nephretomy
Tumor Size:
  Greatest dimension: 18 cm
  Additional dimensions: 17 x 7 cm
Patient Age: ≥5 years
Histologic Type: Neuroblastoma
Degree of Differentiation (neuroblastic component): Poorly differentiated (previous pretreatment biopsy)
Mitotic-Karyorrhectic Index (MKI) (neuroblastic component): High (>200 per 5000 cells; >4%)
Treatment History: Preoperative therapy given
Treatment Effect: Present
Percent tumor necrosis: 10%
Percent therapy-induced cytodifferentiation: 5%
International Neuroblastoma Pathology Classification (INPC): (previous biopsy S14-xxxx)
Unfavorable histopathology
Neuroblastoma (Schwannian stroma-poor)
Poorly differentiated subtype, low or intermediate MKI, >18 months old
Tumor Extent:
  Primary Tumor
  Encapsulated
Regional Lymph Nodes: 3
Number of Lymph Nodes Involved: 0

References

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47. Wilms Tumor

Heather Rytting, MD; Shelley Caltharp, MD; Beverly Rogers, MD; Hong Yin, MD

Background

Wilms tumor (nephroblastoma) is the most common malignant kidney tumor of childhood and typically affects 1 to 4 year olds.[1] Infants may have Wilms tumor, but mesoblastic nephroma, malignant rhabdoid tumor, and clear cell sarcoma are also important considerations in the first year of life. These grossing instructions can be adapted to other pediatric kidney malignancies but they are written specifically for Wilms tumor.

The usual surgical procedure for Wilms tumor is unilateral ureteronephrectomy with lymph node sampling.[2] Histologic grade and accurate staging of the tumor requires meticulous gross documentation with tumor section mapping. Grossing technique can significantly impact patient treatment.[3] Molecular studies help stratify patient treatment categories, so it is important to obtain appropriate tissue and sections for these studies when possible.[4,5]

Staging system and central review

The Children's Oncology Group (COG) staging system below, adapted from the April 2017 College of American Pathologists (CAP) protocol, makes it clear that correct gross documentation is necessary for accurate staging.[5]

I. Tumor is confined to kidney with complete resection and negative margins. Renal capsule is intact. Tumor is not present in renal sinus vessels. There is no or minimal infiltration of renal sinus connective tissue. Tumor was not biopsied prior to resection.

II. Tumor has extended beyond the kidney but is completely resected with no residual abdominal disease. The tumor penetrates renal capsule into perirenal tissues but does not reach the surface of the specimen. It is present in vessels and lymphatics in renal sinus or extends into renal vein. There is bulky or extensive disease in the renal sinus connective tissue. Tumor was not biopsied prior to resection.

III. Tumor has likely not been completely resected. Tumor extends to surface of the specimen. Tumor is present at margins. Tumor is present in intraabdominal or pelvic lymph nodes. There is tumor spillage including tumor removed in multiple pieces. Peritoneal implants are present. Tumor was biopsied prior to resection.

IV. There is distant metastatic disease which includes hematogenous metastases or nodal metastases outside of the abdomen.

V. Bilateral Wilms tumors. Each tumor is given its own substage.

The Wilms tumor staging system was developed by Dr. Bruce Beckwith, who initiated pathologic central review of Wilms tumors through the National Wilms Tumor Study, a program that significantly advanced care for Wilms tumor patients.[1,6] It is still common to submit these tumors to COG for central review. Careful gross documentation and photography enhances central review and consultation. Distinguishing stage I from stage II can be particularly difficult and may be discrepant on central review. Discrepancies mostly relate to the definition and extent of renal sinus involvement.[5] This is partly due to the anatomy of the renal sinus. The renal capsule is incomplete at the renal sinus, so minimal involvement of renal sinus fat or connective tissue does not necessarily indicate that the tumor should be upstaged from I to II. Currently stage II sinus involvement is defined as lymphvascular invasion in the renal sinus or extensive soft tissue involvement of the renal sinus. Both criteria can be subjective, so central review continues to be important. Careful sampling and documentation of the tumor relationship to the renal hilum is therefore crucial.

Gross description/what to expect

Tumors may be solid or cystic. They are often large, bulky, tan-white, very soft, and well circumscribed (Figure 47-1).

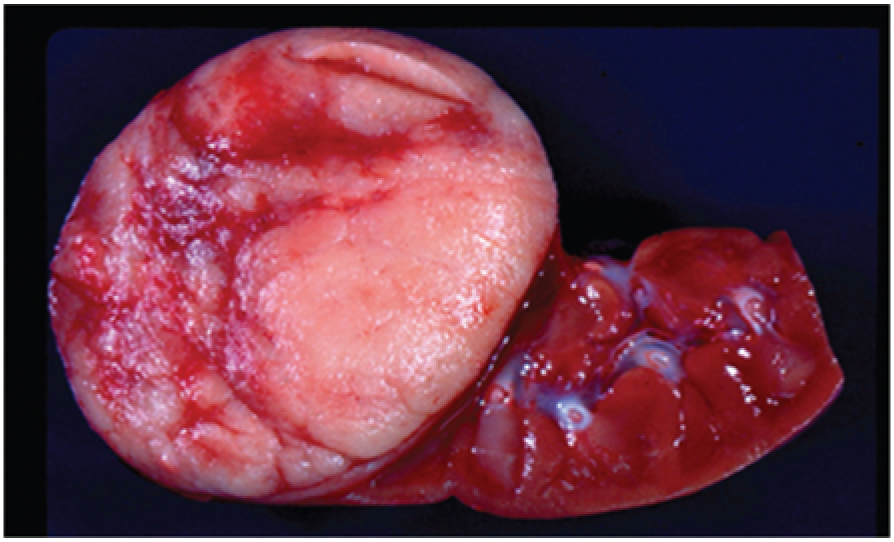

Figure 47-1. Typical Wilms tumor, fresh specimen with bulging tumor surface. (Image courtesy of Carlos Abramowsky, MD.)

The softness and discohesive nature of tumor cells make fresh handling difficult and can introduce staging artifacts. Tumor cells are easily dragged along specimen surfaces, and this should not be interpreted as positive margins. Manipulating the fresh specimen can also artificially displace tumor into renal vessels. For these reasons, a limited number of cuts are made, and the specimen is fixed prior to complete sectioning, making a 2-day gross processing time reasonable. Large tumors markedly distort the kidney and involve the hilar structures, making it difficult to find landmarks. Multicentric tumors occur in 5% to 10% of patients, and each tumor needs to be sampled and documented. Pale ill-defined areas in the adjacent kidney often indicate nephrogenic rests. Nephrogenic rests may transition to hyperplastic rests and Wilms tumor, and are present in a large number of cases (25-50%). Grossly and microscopically, nephrogenic rests, hyperplastic rests, and Wilms tumor represent a spectrum of lesions without clear diagnostic criteria between categories (Figure 47-2). In order to best categorize the lesions, microscopic and gross findings need to be correlated. In general, perilobar nephrogenic rests occur in the peripheral cortex and are ill defined, tan, and wedge shaped. Intralobar nephrogenic rests have a similar appearance but may occur anywhere in the kidney.[1,5-7] Hyperplastic rests are more rounded but not expansile and lack a capsule. Wilms tumors tend to be spherical and have a fibrous capsule. Microscopically, nephrogenic rests bear a resemblance to nephrogenic blastema or the fetal nephrogenic zone. Microscopically, Wilms tumor and hyperplastic rests are essentially identical.

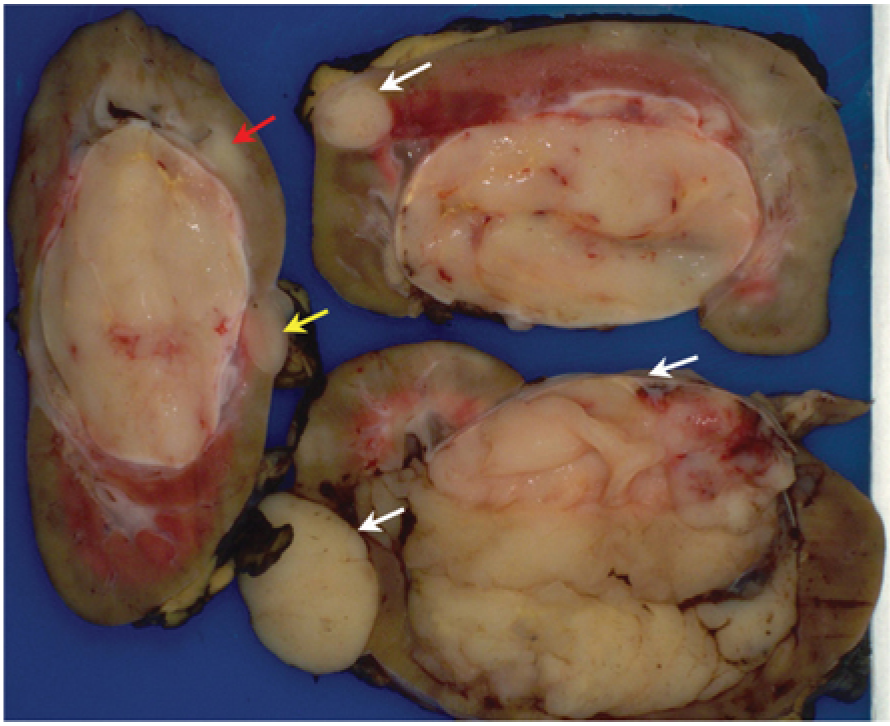

Figure 47-2. White arrows – multicentric Wilms tumors; red arrow – nephrogenic rest; yellow arrow – hyperplastic nephrogenic rest.

Advanced-stage tumors may be treated prior to resection and tumor response to therapy, or posttreatment histologic classification may be necessary. Partial nephrectomies are appropriate for bilateral tumors, treated tumors, or small tumors not involving the hilar structures. For bulkier tumors, a radical nephrectomy or simple nephrectomy may be performed. Radical nephrectomy includes perirenal soft tissue and can include the adrenal gland. Lymph node dissections may also be performed.[2] Wilms tumors often grow into the ureter or renal vein, so ureterectomy or phlebectomy with tumor thrombectomy may also be performed. In Figure 47-3, tumor fills the renal pelvis, growing in a botryoid pattern, and fills and distends the ureter. There is also extensive infiltration of the renal hilum and sinus.

Figure 47-3. White arrow – tumor growing into distending ureter; red arrow – botryoid tumor nodules distending renal pelvis; yellow arrow – tumor growing into renal hilum and replacing sinus soft tissue (stage II).

In order to properly stage the tumor, careful communication with the surgeon or review of operative notes concerning capsular disruption, tumor spillage, and presence of tumor at margins may be necessary.

Specimen Receipt and Initial Preparation[5,8]

The specimen is most often received intact and fresh, which is recommended. Never strip the renal capsule from pediatric kidney specimens. Frozen section diagnosis is generally not encouraged for renal tumors in pediatrics as the limited sampling and limited detail of frozen section can lead to errors. Frozen section is appropriate if information will alter operative management. It may also be appropriate to assure that viable rather than necrotic tumor is aliquoted for ancillary studies. The specimen history should include laterality, procedure type, and specimen orientation. Specimens should be handled as soon as possible or refrigerated until gross examination can begin. Photograph, measure, and weigh the specimen. Accurate weight of the specimen is critical, as staging and treatment can be altered by specimen weight. Before inking the external surface, identify the hilum, which will contain from anterior to posterior, the renal vein, artery, and pelvis with ureter (Figure 47-4). The vessels and ureters may branch or be duplicated so more than three structures may be ligated. In order to avoid tumor contamination of these structures, these margins should be submitted en face prior to any initial tumor sectioning.

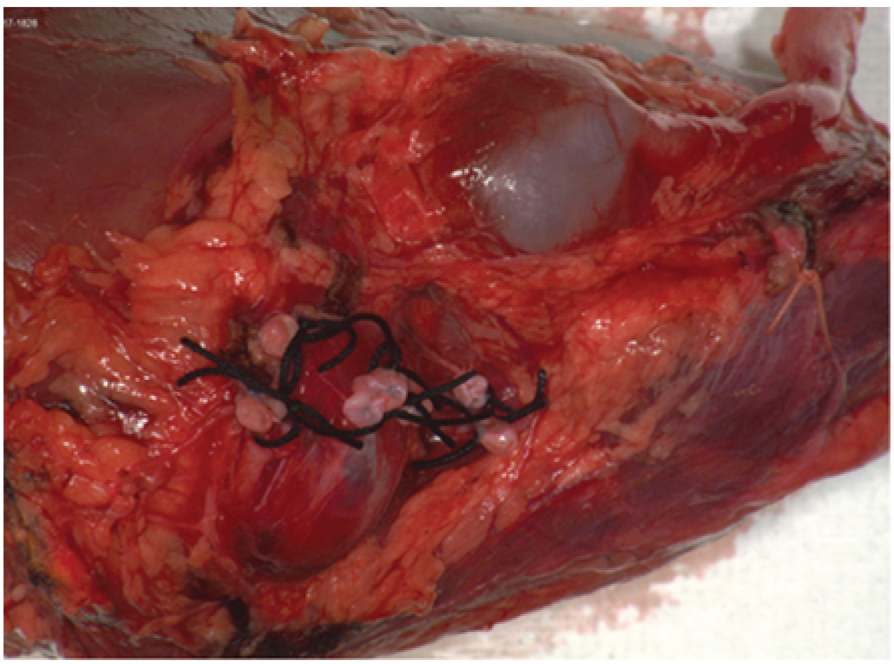

Figure 47-4. Hilar vessels and ureter are often ligated and are easier to identify before inking the specimen. En face, shave margins of ureter and vessels should be submitted prior to sectioning. In this photo there is no macroscopic evidence of tumor at these margins.

Look for any orientation provided by the surgeon. Note if tumor has penetrated to the specimen surface (stage III, pending microscopic confirmation), distorts the hilum replacing the sinus (stage II, pending microscopic confirmation), or is present at any margins (stage III, pending microscopic confirmation) including those of the ureter, artery, or vein. Submit en face margins of artery, vein, and ureter prior to inking.

Ink the surface of the specimen one color and use a second color to overlay areas suspicious for involvement of the specimen surface or positive margin as these would denote stage III tumors and need microscopic confirmation. Allow the ink to dry completely before cutting specimen. This takes 1 to 2 minutes. Ink can also be dried by using acetic acid or other appropriate drying agent. Bivalve the specimen using the ureter as a guide so that the renal pelvis, hilum, and sinus can be seen on cut surface. This cut is typically easiest going from ureter towards the capsule. The relationship to the tumor to the hilar structures can then be assessed (Figure 47-5).

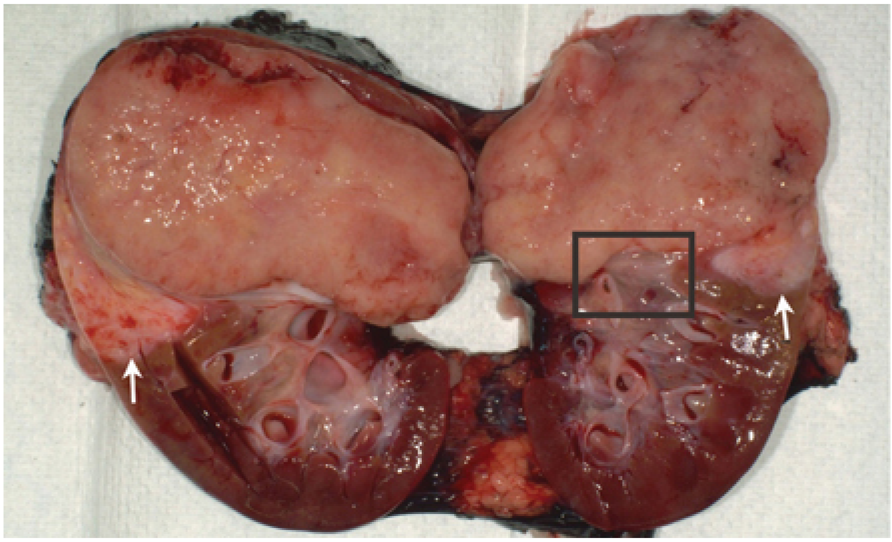

Figure 47-5. Tumor has been bivalved through the ureter and collecting system so that relationship to the hilum can be seen. It is grossly apparent that there is extensive renal sinus involvement. Sections from this area (black box) will confirm stage II tumor. White arrows indicate a nephrogenic rest in association with the tumor. The pelvicaliceal system is dilated indicating hydronephrosis.

The hilum is the region of the kidney which contains the collecting system, vessels, fat, and ureter. The pelvis is the funnel-shaped portion of the collecting system that empties into the ureter. The sinus is the fat and connective tissue surrounding the pelvis and ureter. The sinus contains blood vessels and lymphatics, and involvement of these vessels will upstage the tumor to stage II. The renal capsule is incomplete at the hilum, so renal sinus connective tissue and fat is continuity with renal cortex in this region (Figure 47-6).

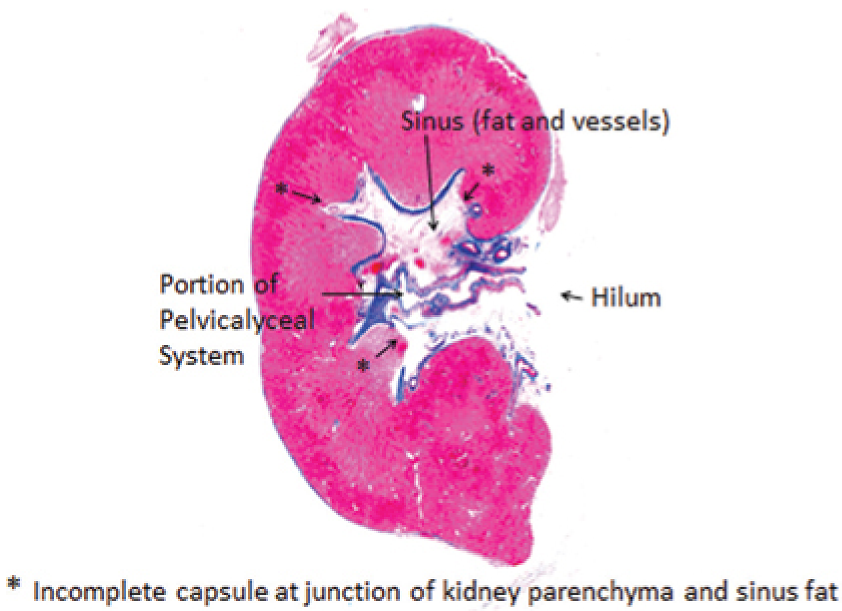

Figure 47-6. Trichrome-stained whole mount of kidney showing incomplete renal capsule in the hilum. (Image courtesy of Carlos Abramowsky, MD.)

For that reason, tumor does not need to invade through the renal capsule to extend into sinus adipose tissue, which is why minimal sinus involvement by tumor is still stage I.[1,4] After the initial cut to expose the hilum, make additional 2- to 3-cm thickness cuts through the tumor, keeping the cuts in order. It is typical for the tumor parenchyma to bulge above the cut surface and for a stretched thin capsule to retract away from the incision. Therefore, the tumor slices need to be at least 2 cm thick in order to preserve the anatomy. After the slices are made, a pilot section of tumor can be submitted for preliminary review and diagnosis. Reserve and freeze fresh

tissue for ancillary studies. Two aliquots of tumor and two aliquots of normal kidney are suggested. One gram of tissue (1 cm^3) per aliquot is optimal. Photograph the tumor slices, especially those you plan to select for tumor mapping. To avoid sectioning artifact, handle the slices as little as possible and fix overnight in formalin prior to complete sectioning. The specimen slices should be pieced back together, wrapped in gauze, and then fixed in formalin. Refrigerated overnight fixation is optimal.

Tumor Mapping and Sectioning[5,8]

After fixation examine the tumor slices for the following:

1. Single or multicentric tumors (5-10% are multicentric). Measure each tumor and document the maximum dimension of each tumor.
2. Involvement of hilar structures including bulky disease distorting the hilum and involving the sinus, possible stage II
3. Surface penetration or involvement by tumor, stage III
4. Extension into renal vein, stage II
5. Growth into but limited to renal pelvis and ureter lumen, stage I
6. Transected tumor at margins, stage III
7. Pale areas away from tumor or adjacent to tumor that suggest possible nephrogenic rests

Using a drawing or specimen photograph, make a tumor map documenting each section (Figure 47-7). This map is critical for staging and determining focal or diffuse anaplasia. It is also helpful should central review or consultation be needed. Obtain enough sections to assess histology and to stage the tumor accurately.

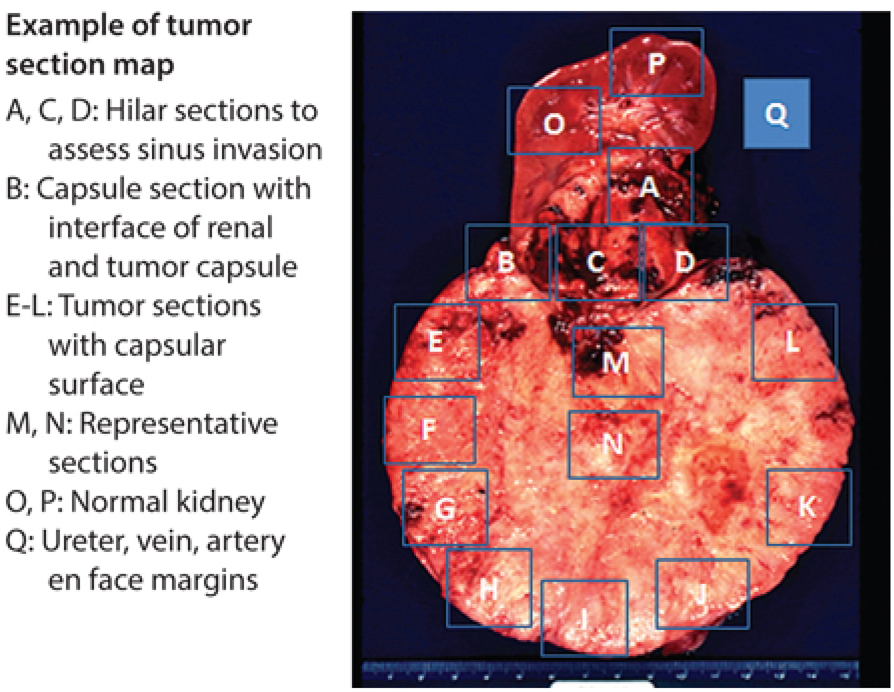

Figure 47-7. Gross invasion of sinus and likely capsular invasion. (Image courtesy of Carlos Abramowsky, MD.)

Example of tumor section map

A, C, D: Hilar sections to assess sinus invasion

B: Capsular section with interface of renal and tumor capsule

E-L: Tumor sections with capsular surface.

M, N: Representative section

O, P: Normal kidney

Q: Ureter, vein, artery, enface margins

Recommended sections follow[5,8]

1. The number of tumor sections should equal the largest tumor dimension in centimeters. A 10-cm tumor should have 10 sections that contain tumor. This number of sections will allow for assessment of percent necrosis and histologic pattern in posttreatment specimens. It will also allow detection of focal or diffuse anaplasia. The specimen map can be critical in determining focal versus diffuse anaplasia as the distinction requires knowing if sections are contiguous, if anaplasia is surrounded by favorable histology tumor, or if anaplasia is near the capsular surface or a margin.

2. One to three central tumor sections should be obtained as part of the 10 tumor sections.

3. The remainder of the sections should be taken to show important structures such as the specimen surface or sinus tissue adjacent to tumor.

4. Submit extrarenal tissues such as adrenal gland and all lymph nodes from any lymph node resection.

5. Submit several sections of residual normal kidney including any areas suspicious for nephrogenic rests. Nephrogenic rests are common, and the type of rest (perilobar or intralobar) may indicate a syndrome or predisposition to multiple or bilateral tumors.

6. Take sections showing the renal capsule at the interface of tumor and cortex to try to delineate pseudocapsule from capsule.

7. Take sections of any satellite tumors or nodules.

8. Submit en face shave margins of ureter, artery, and vein.

9. If there is bulky disease distorting the hilum, take sections from this area to document sinus involvement by tumor.

Example report

Gross description

Received fresh in a container labeled with the patient name, medical record number, and "right kidney tumor" is a right nephrectomy specimen with smooth covering containing a small amount of perirenal adipose tissue and adrenal gland. Renal vessels and ureter are ligated with black sutures and are free of tumor involvement. The kidney is distorted by a tumor which expands and replaces the upper pole and mid-portion of the kidney. The surface is smooth, with no areas of tumor penetration or surface involvement either along the capsule or within the pelvic tissue. The specimen measures 12.5 cm superior to inferior, 7.5 cm medial to lateral, and 5.0 cm anterior to posterior. It weighs 257 g. The segment of ureter is 7.5 cm long and 0.3 cm in diameter. The adrenal gland measures 1.5 cm in greatest dimension, is not involved by tumor, and is distinct from the kidney. The specimen surface is inked black. A cross-section through the ureter and renal hilum contains a white-tan bulging well-circumscribed tumor replacing the superior pole, mid kidney, and the superior portion of the renal sinus. Maximum tumor dimension is 7.6 cm. The nearest capsular surface is 0.3 cm from the tumor. An ill-defined pale wedge-shaped area involves the renal cortex adjacent to the tumor. The remaining kidney parenchyma is without focal lesions. No lymph nodes are received. Two portions of fresh kidney and two portions of fresh tumor are frozen and stored at -80°C for ancillary studies if needed.

Section code

A: En face margins of renal artery, vein, and ureter

B: Representative adrenal gland

C–D: Normal kidney

E: Pale area adjacent to tumor (possible nephrogenic rest)

F–L: Eight tumor sections, diagram attached

F , G, H: Renal sinus with tumor

I: Central sections of tumor

J, K: Tumor closest to renal capsular surface

L, M: Additional sections of tumor with capsular surface

Example diagnosis

Right Kidney, Radical Nephrectomy with Adrenal Gland:

- Nephroblastoma (Wilms tumor) with favorable histology arising in association with perilobar nephrogenic rest
- Specimen weight 257 g
- Tumor size 7.6 cm
- Stage II
- Extensive soft tissue involvement in renal sinus
- No lymphvascular invasion identified
- No renal capsular invasion
- Margins negative
- Adrenal gland without abnormality

Synoptic report

Procedure: Radical nephrectomy
Specimen Weight: 257 g
Laterality: Right
Tumor size, Greatest dimension: 7.6 cm
Tumor focality: Unifocal
Tumor Extent:
  Gerotas Fascia: Intact
  Renal Sinus: Tumor more than minimally involves renal sinus soft tissue
  Renal Vein: No renal vein invasion
  Renal Capsule: No extension beyond renal capsule
  Adjacent Organ Involvement: No tumor extension into adjacent organs
Margins: Uninvolved by tumor
Histologic Type: Wilms tumor, favorable histology
Nephrogenic Rests: Focal perilobar
Posttherapy Histologic Classification: No known preoperative therapy
Regional Lymph Nodes: No nodes submitted
COG Staging System: Local Stage II, Tumor extends beyond kidney due to more than minimally involved renal sinus soft tissue but is completely resected.

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48. Skin

Ruifeng Guo, MD, PhD; Mark A. Cappel, MD

Introduction

Skin pathology specimens may be received after a variety of procedural techniques performed by the clinical providers while evaluating and treating skin cancer, including skin biopsies, excisions, lesion removals, and destructions.

Skin cancer is a common malignancy and, in order of incidence, this includes basal cell carcinoma,[1] squamous cell carcinoma[2] (often termed nonmelanoma skin cancer), and malignant melanoma.[3] Merkel cell carcinoma[4,5] is another notable type of skin cancer, which is less common yet has a particularly poor prognosis. Due to the high incidence of skin cancer and the accessibility of the cutaneous surface, skin biopsies, and other dermatologic procedures are frequent.

The intent of a skin biopsy procedure is to obtain tissue from a lesion for the sole purpose of diagnostic histopathologic examination. Partial-thickness skin biopsies sample a portion of skin and do not penetrate below the dermis, whereas full-thickness skin biopsies penetrate deep to the dermis into the subcutaneous tissue. Tangential biopsy techniques refer to various partial-thickness sampling procedures (shave, scoop, saucerization, curette) whereby epidermal tissue with or without underlying portions of dermis are removed. Conversely, punch biopsies obtain a full-thickness cylindrical skin sample using a specific punch tool. Incisional biopsies also remove a full-thickness sample, though with a sharp blade making a vertical incision or wedge.

During many other dermatologic procedures, such as excisions, lesion removals, and destructions, the skin tissue is also frequently submitted for histopathologic examination but diagnosis is not the sole purpose of such procedures. Excisions are defined as a full-thickness removal of a skin lesion including margins. Shave removals are partial-thickness samples and use transverse incision or horizontal slicing to remove epidermal or dermal lesions. Skin tag removals are self-explanatory, whereby a scissors or a blade removes the pedunculated papules. Destructions are the ablation of skin lesions by any method including electrosurgery, cryosurgery, laser, or chemical treatments.

Understanding the variety of dermatologic procedures and the intention of the dermatology provider in obtaining each skin sample is essential in order to properly handle and prepare the specimen for microscopic evaluation. This in turn fosters an accurate pathologic diagnosis and a thorough assessment of the necessary staging parameters that pertain to skin cancer. Complete pathologic examination is necessary for the correct staging of skin cancer, which provides important prognostic information and thereby directs future patient care and treatment.

I. Indications for obtaining a skin specimen

The clinical presentation for skin cancer is variable, as skin cancer can present as a flat macule or patch, an elevated papule or plaque, or a dermal or subcutaneous nodule. Skin cancers may be symptomatic (tender, bleeding, itchy), asymptomatic, have surface changes (scaly, crusted, hyperkeratotic), have a smooth surface, or be variably colored (erythematous or violaceous, pigmented or flesh-colored). The degree of clinical suspicion, lesion size, anatomic location, and potential cosmetic outcome of a subsequent biopsy scar all play a role in the clinician's decision on the type of sampling procedure. Because of these considerations, many diagnostic and staging pitfalls exist, particularly with frequent partial skin biopsies that do not include the complete depth and/or breadth of the lesion.

1. Clinical concern for a potential skin cancer will initiate a skin biopsy procedure.

A. Tangential biopsy is typically completed for a presumed superficial skin lesion (involving the epidermis to superficial dermis).

B. Punch biopsy is generally completed in order to assess the full depth of the tumor, especially if there is clinical concern for a lesion substantially involving the dermis and/or superficial subcutis. Punch biopsy sites are frequently sutured closed; therefore, at times this technique may be preferred for a potentially improved cosmetic result from the biopsy scar when compared to other tangential biopsy techniques.

C. Incisional biopsy is often utilized to sample a representative wedge of skin in a large clinical lesion, such as a subcutaneous nodule or wide-diameter pigmented lesion.

2. A biopsy-proven diagnosis, a clinically certain diagnosis, or a symptomatic lesion may initiate an excision, shave removal, skin tag removal, or destruction (all depending on the diagnosis).

A. Excisions are completed when a full-thickness skin specimen including margins around the lesion are indicated.

B. Shave removals are completed when only a partial-thickness skin specimen is required (an epidermal and/or a dermal lesion).

C. Skin tag removals are completed in order to remove symptomatic skin tags.

D. Destructions are completed when no additional skin specimen is necessary to make the diagnosis, though at times the curettage portion of such a specimen may be sent for pathologic confirmation.

II. What do you expect to see in a skin specimen?

Based on the above indications for obtaining skin specimens, the findings may in fact show a type of skin cancer, but many times benign or premalignant lesions that can mimic skin cancer are biopsied. Frequent reasons for skin biopsies are those sent as possible nonmelanoma skin cancer (basal cell carcinoma or squamous cell carcinoma), which dermatology providers are quite apt at identifying, but in this scenario benign or premalignant keratoses are also frequently biopsied. Another common situation is skin biopsies sent as possible melanoma, which is often challenging to clinically distinguish from benign pigmented lesions; therefore, solar lentigines, pigmented keratoses, and benign and atypical nevi are frequently biopsied in this scenario.

If a biopsy does show skin cancer, then it is a matter of determining the type of skin cancer, the histopathologic subtype as applicable, and any important staging or prognostic factors for that tumor. The depth of involvement of the tumor is an important feature for all skin cancer. For example, the use of Clark level had been important in the prior staging and prognosis of malignant melanoma (Clark I = only epidermis involved/in-situ, Clark II = papillary dermis superficially involved, Clark III = papillary dermis fully involved, Clark IV = reticular dermis involved, Clark V = subcutaneous tissue involved). For malignant melanoma, Clark level has since been replaced by Breslow depth, which measures in millimeters to the deepest malignant cell from the top of the epidermis (granular layer) or from the base of the ulceration in an ulcerated melanoma.

III. Gross examination of skin specimens

The first step in gross examination of skin specimens is to confirm the type of specimen (shave, punch, incision, excision, or curettage), as this will dictate how a sample should be inked and sectioned. If the lesion can be identified grossly, this will help to direct those grossing the specimen to cut representative sections through the visible lesion. However, since skin biopsies can be very small and certain types of skin lesions may not have a distinct outline, it may not always be possible to precisely visualize the lesion during grossing. Small skin biopsies can also be too small to bisect and therefore may need to be submitted in toto. Excisional specimens may be tagged with a suture or inked by the dermatology provider. If not already done so by the clinician, it is important to designate this point as a specific clock-face orientation (eg, 12 o'clock).

IV. Sectioning techniques: step-by-step description

1. Tangential biopsy specimen (shave, scoop, saucerization)

If the clinician also is requesting margins, then inking the peripheral and deep margins is advised. Depending on the size of the specimen, the specimen may be bisected, trisected, or quadrisected. Although not the ideal, if

the specimen is too small to section, it may be submitted in toto (Figure 48-1).

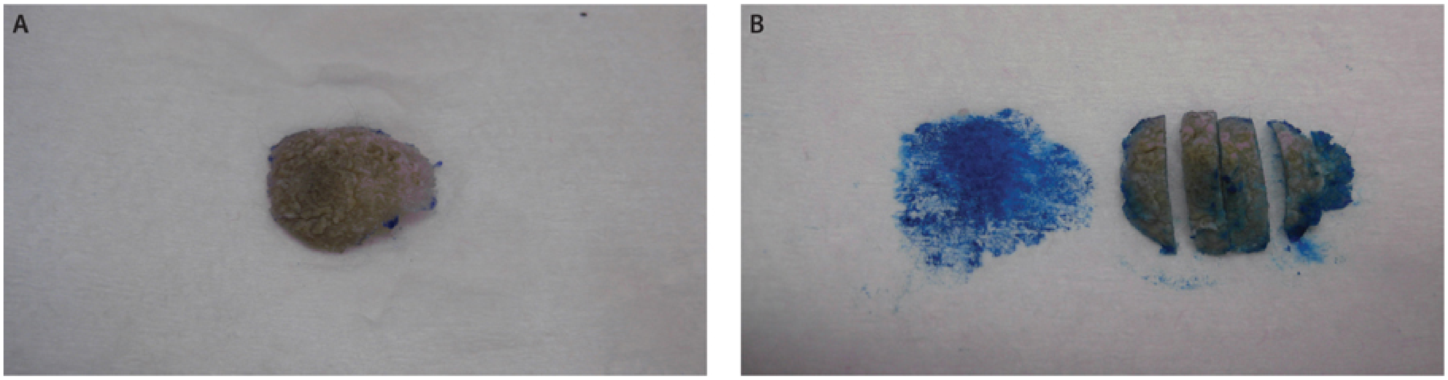

Figure 48-1. A, B, Example of shave biopsy, serially sectioned.

2. Punch biopsy and punch excision specimen

If the clinician also is requesting margins, then inking the peripheral and deep margins is advised. Depending on the size of the specimen, the specimen may be bisected or trisected. Although not the ideal, if the specimen is too small to section, it may be submitted in toto (Figures 48-2 and 48-3).

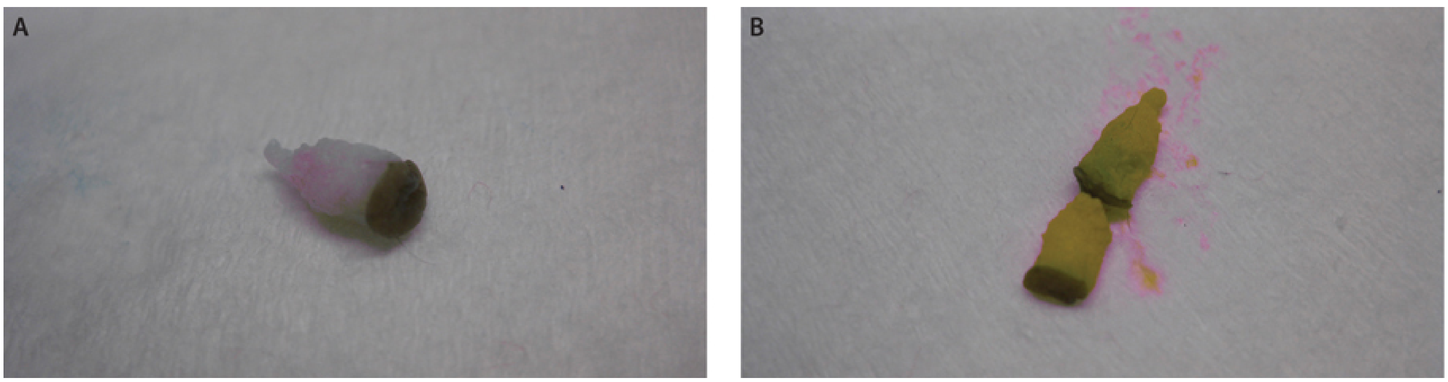

Figure 48-2. A, B, Example of punch biopsy, bisected.

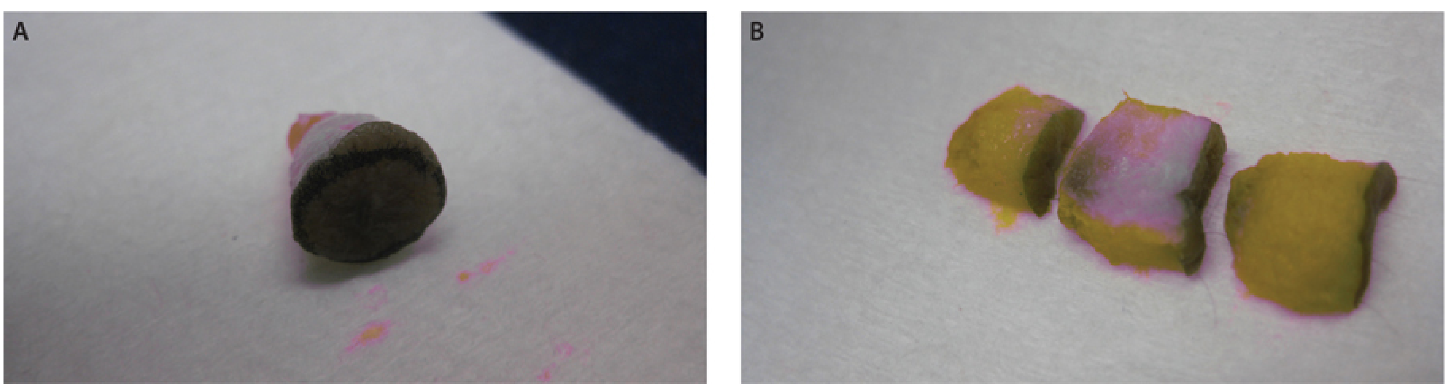

Figure 48-3. A, B, Example of punch excision, serially sectioned.

3. Incisional biopsy specimen

Incisional specimens may be sectioned longitudinally (parallel to the long axis) or bread-loafed (sectioned perpendicular to the long axis), since by definition the peripheral margins are expected to be positive in an incisional biopsy specimen.

4. Excision specimen

Excisional specimens should be oriented as a clock-face if designated with a nick, suture, or ink by the clinician. The peripheral and deep margins should be inked. One color of ink may be used if the excision is unoriented. If the specimen is oriented, it is recommended to use three to four colors of ink at the periphery in order to accurately map out any positive margins. An excision specimen may be bread-loafed with tips cut for peripheral en face sections, which often depends on clinician preference (Figures 48-4 and 48-5).

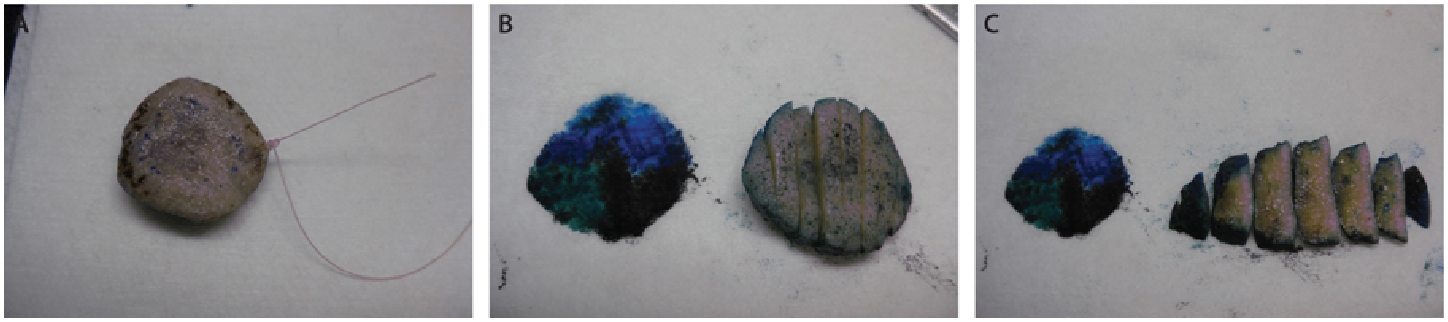

Figure 48-4. A-C, Example of circular-shaped excision, oriented, inked, and serially sectioned.

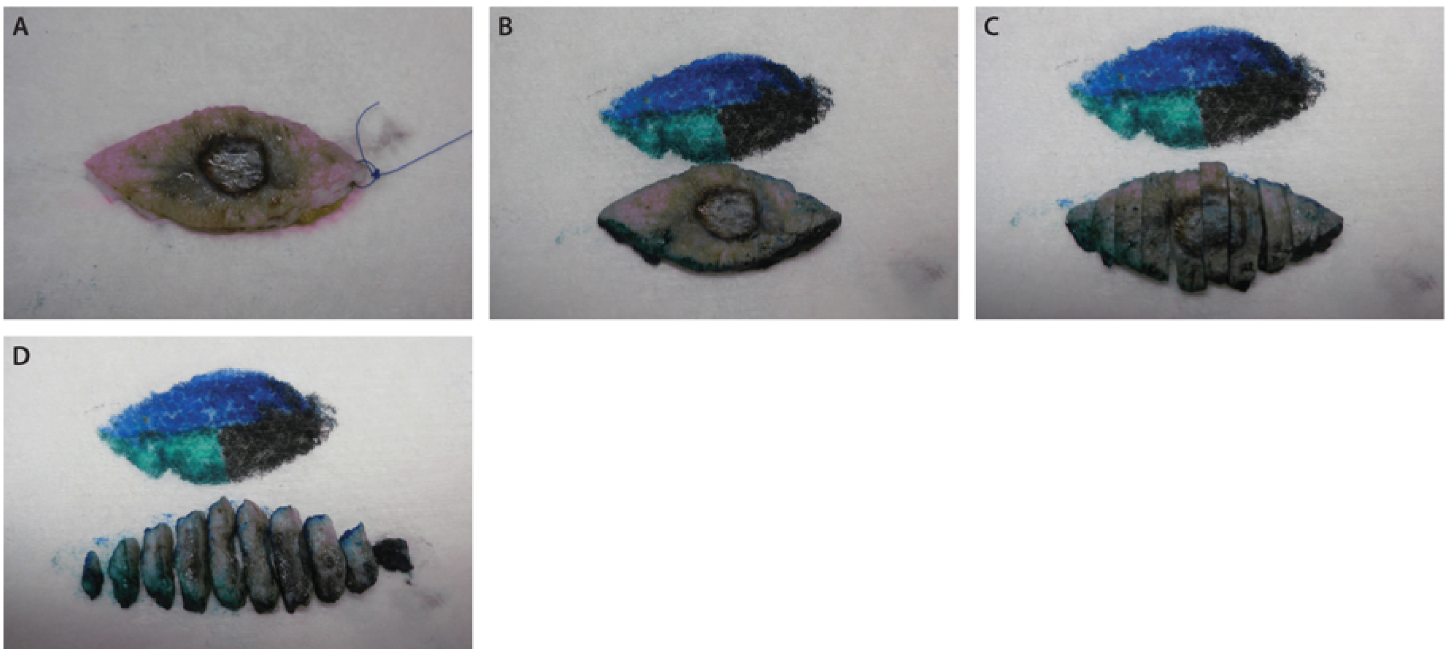

Figure 48-5. A-D, Example of elliptical excision, oriented, inked, serially sectioned, and laid out perpendicularly.

5. Shave removal specimen

Clinicians often request margins; therefore, inking peripheral and deep margins is advised. Depending on the size of the specimen, the specimen may be bisected, trisected, or quadrisected.

6. Skin tag removal specimen

Inking for margins is unnecessary for skin tag removals. Depending on the size, skin tags may be bisected or submitted in toto.

7. Lesion destruction

After cryotherapy or electrocautery and curettage, the curettage specimen may be sent for pathologic confirmation. This usually consists of multiple small fragments that may need to be filtered and submitted in toto without further sectioning.

V. Gross descriptions using paragraph system

Skin specimen gross descriptions should include:

• The type of specimen (shave, punch, incision, excision, skin tag, curettage)

- The dimensions of the specimen (length x width x depth)
- The appearance and the dimension of the gross lesion if visible (length x width x depth)
- The orientation of the specimen (example: suture designated as 12 o'clock)
- The inking of the specimen (example: green ink 12-3 o'clock, blue ink 3-6 o'clock, red ink 6-9 o'clock, black ink 9-12 o'clock)

Example of a gross description for melanoma excision

Received in formalin (or fresh), labeled as "left forearm" with the patient's name and medical record number, is a 5.5 x 3.2 cm skin ellipse excised to a depth of 1.2 cm. A suture marks the superior (proximal) tip of the excision, designated as 12 o'clock. The excision margins are inked as follows: green ink 12-3 o'clock, blue ink 3-6 o'clock, red ink 6-9 o'clock, black ink 9-12 o'clock. A centrally located pigmented lesion with irregular border (or a centrally located scar) is present, 0.8 x 0.7 cm in greatest dimension. No ulceration, satellite pigmentation or satellite nodule is grossly identified. The margins are grossly uninvolved by the pigmented lesion (or scar), and the closest peripheral margin at the 12-3 o'clock aspect is 1.2 cm away. The deep margin is composed of grossly unremarkable subcutaneous adipose tissue. The specimen is representatively submitted as follows.

Block summary

A1: 12 o'clock tip, shaved

A2: 6 o'clock tip, shaved

A3-A6: Central pigmented lesion (or scar), serially sectioned from superior to inferior, entirely submitted with adjacent margins, perpendicular sections

A7: Representative section of grossly unremarkable skin between the pigmented lesion (or scar) and 12 o'clock tip with adjacent margins, perpendicular section

A8: Representative section of grossly unremarkable skin between the pigmented lesion (or scar) and 6 o'clock tip with adjacent margins, perpendicular section

VI. Common pathologic findings in skin specimens

The following types of skin cancer may be identified:

1. Basal cell carcinoma (superficial, nodular, micronodular, or infiltrative patterns)
2. Squamous cell carcinoma (in situ or invasive with degree of differentiation)
3. Malignant melanoma (in situ or invasive with Breslow depth)
4. Merkel cell carcinoma

Many skin tumors are transected at the base of the skin biopsy specimen. Therefore, skin biopsies do not always give an accurate depth of invasion of the tumor. When this occurs, it is recommended to render a diagnosis with that caveat. For example: malignant melanoma, at least 1.5 mm Breslow depth; or squamous cell carcinoma, at least in situ. Then it is recommended to make a comment stating that the base of the tumor is transected and to correlate the final depth seen on the subsequent excision specimen.

VII. Common potential staging pitfalls and solutions

A. Basal cell carcinoma

Histologic subtyping of basal cell carcinoma (BCC) is helpful for clinicians in order to decide the best treatment modality.[6] For example, nodular-type BCC is more commonly circumscribed, while micronodular-type or infiltrative-type BCC has a more irregular growth pattern, making it more difficult to achieve clear margins (Figure 48-6). On the other hand, superficial-type BCC shows predominant radial spread of the tumor that could be more subtle and discontinuous. In addition, other unusual features, including very large size, deeply infiltrative pattern into subcutaneous tissue, and perineural invasion, should be documented if pathologically identified.[7-11] Additionally, squamous differentiation is sometimes prominent in basal cell carcinoma. Sometimes the terms basosquamous carcinoma or metatypical basal cell carcinoma are used to describe tumors that appear to show both squamous and basal cell differentiation. Historically, these terms implied a more aggressive behavior, but further study has shown that they usually have similar outcome to other

nonmelanoma skin cancers.[12,13] The presence of distinct components of basal cell carcinoma and squamous cell carcinoma is the key for differential diagnosis.[12,13]

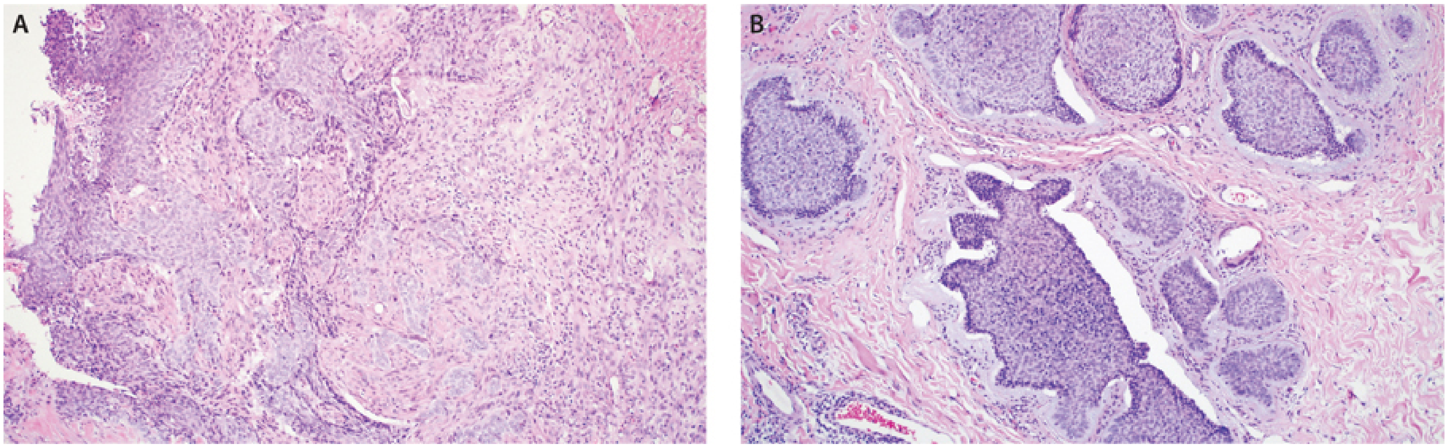

Figure 48-6. Basal cell carcinoma. A, Infiltrative type. B, Nodular type.

B. Squamous cell carcinoma

Cutaneous squamous cell carcinoma (SCC) can sometimes show aggressive clinical behavior including both local destructive growth and metastasis.[14-17] Therefore, attention should be paid to report the histologic features that could indicate aggressive clinical behavior of the tumor. These features include clinical or gross size of the tumor (>2 cm), histologic differentiation (poor differentiation) (Figures 48-7 and 48-8), depth of invasion >2 mm thickness, perineural invasion, and Clark level >IV.[18-22] Perineural invasion is of particular importance, and the caliber of involved nerve if >0.1 mm should be described, which is associated with nodal metastasis and long-term survival.[11,23] Lymphovascular invasion is uncommon but should be documented when observed.[20,24] In addition, anatomic location is also important to note. For example, SCCs occurring on the ear, nonhair bearing lip, head and neck skin with significant sun damage, or associated with long-term wound/ulcer/inflammation are all considered as high-risk sites for squamous cell carcinoma.[25]

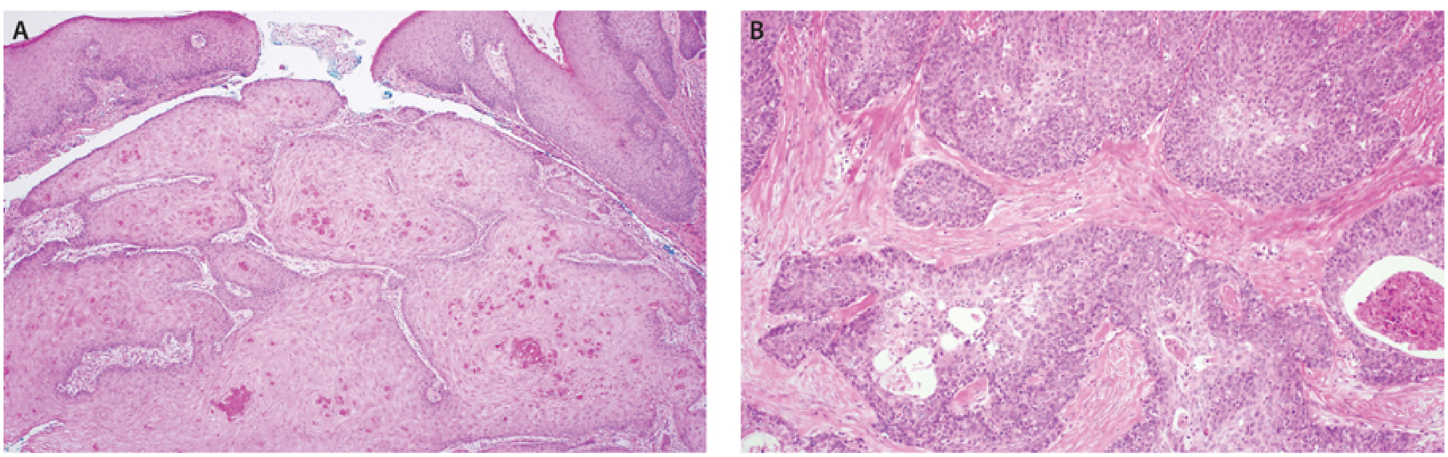

Figure 48-7. Invasive cutaneous squamous cell carcinoma. A, Well differentiated. B, Moderately differentiated.

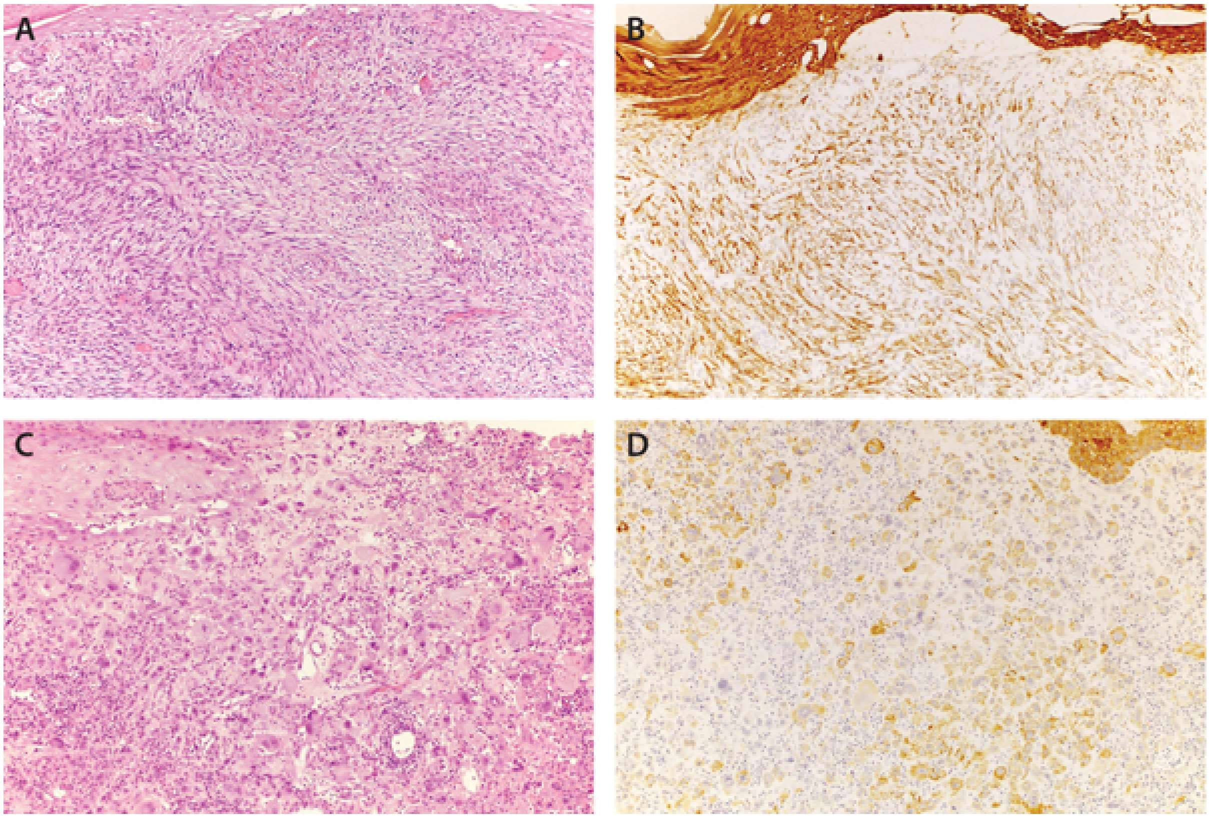

Figure 48-8. Poorly differentiated cutaneous squamous cell carcinoma. A, B, Spindle cell morphology, positive for CK5/6 immunostain. C, D, Epithelioid and pleomorphic morphology, positive for CK5/6 immunostain.

C. Melanoma

Cutaneous melanoma staging is commonly encountered in routine surgical pathology practice. The staging criteria for melanoma have been established, and the details about how to stage melanoma can be referred to the published American Joint Committee on Cancer (AJCC) guidelines or College of American Pathologists (CAP) guidelines.[26] However, inaccuracies in melanoma staging can be frequent, which could have significant clinical consequences. Therefore, the following paragraphs list the common pitfalls in melanoma staging with corresponding solutions.

(a) Histologic subtype

Although it is optimal to recognize different histologic subtypes of melanoma, the melanoma subtype is not the most important prognostic factor. The most common type of melanoma is superficial spreading, followed by lentigo maligna and nodular melanoma. Acral lentiginous melanoma is the most common type of primary melanoma involving the hands and feet. The remaining melanoma subtypes are relatively uncommon (Figure 48-9).[27] However, recognition of desmoplastic melanoma, either pure type (>90% desmoplastic melanoma component) or mixed type, is of particular clinical significance. Desmoplastic melanoma is defined by the presence of prominent desmoplastic stroma with predominant spindle cell morphology. There is variable cytologic atypia and frequent background inflammation including lymphoid aggregates (Figure 48-10). Melanin pigmentation is mostly absent. The cells tend to lose expression of conventional melanocytic markers such as Melan-A/Mart1, HMB45, and tyrosinase, while only maintaining positivity with S100 and SOX10. In contrast to conventional melanoma, desmoplastic melanoma tends to be more deeply invasive and show more common neurotropism (Figure 48-10) with much less locoregional lymph node metastasis.[28-30]

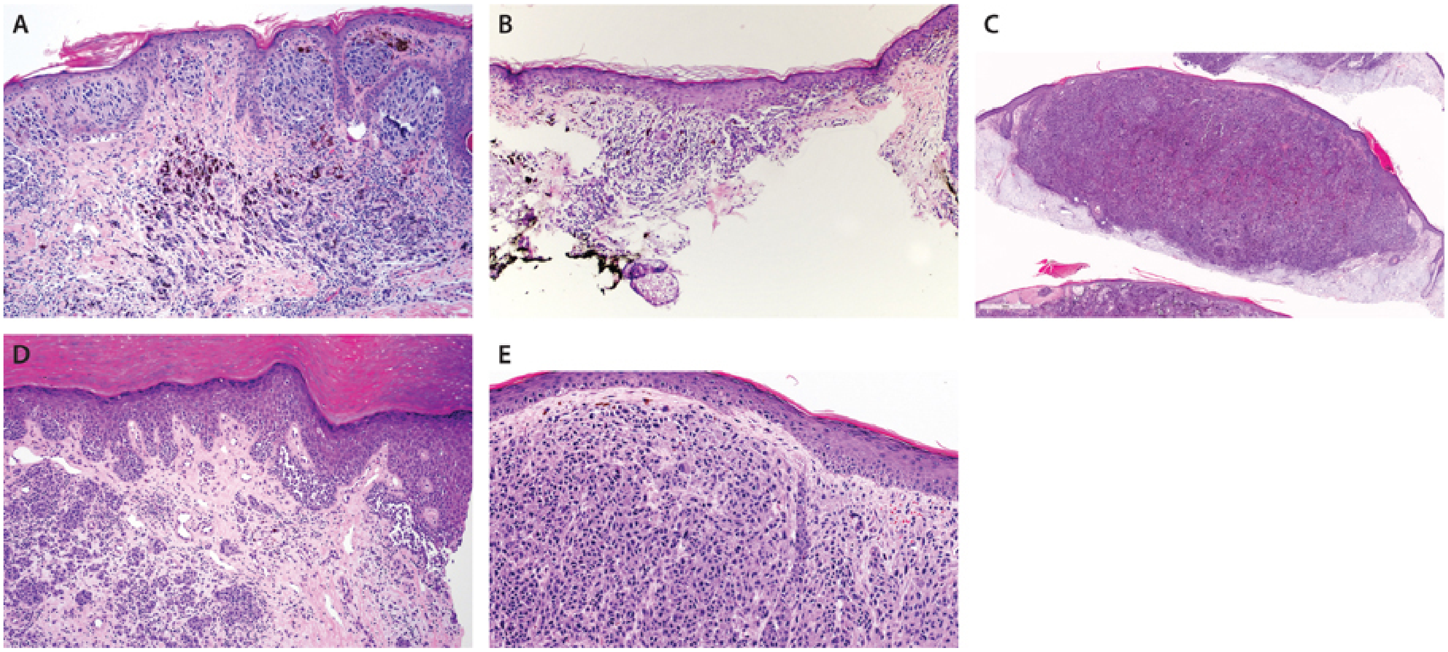

Figure 48-9. Melanoma subtypes. A, Superficial spreading (no invasion in this example). B, Lentigo maligna. C, Nodular. D, Acral lentiginous. E, Nevoid.

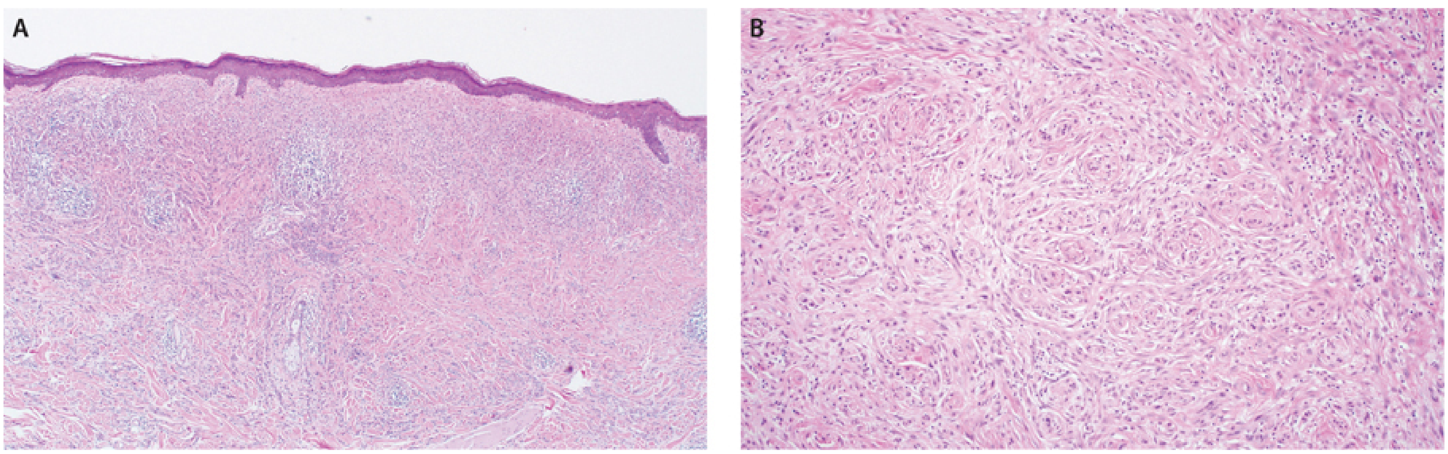

Figure 48-10. A, Desmoplastic melanoma, desmoplastic stroma mimicking fibrotic tissue, recognized by atypical hyperchromatic spindle cells and lymphoid reaction, neurotropism is common. B, Deeper portion of desmoplastic melanoma with extensive neural transformation, an uncommon variant of tumor neurotropism.

(b) Breslow depth and Clark level

Detailed Breslow depth and Clark level evaluation are well described in CAP cancer protocol explanatory notes.[26,27,31,32] The most common error is the incorrect use of the ocular micrometer. Ocular micrometers need to be specifically calibrated based on individual microscopes. When measuring the Breslow depth, the starting point should be based on the top of the epidermal granular layer, while the deepest point should be measured to the deepest invasive tumor cells, which could be melanoma cells identified on hematoxylin-eosin (H&E) or immunostains. The measurement should be performed in a vertical fashion perpendicular to the epidermis as the reference, since an oblique measurement could potentially result in an artificially increased Breslow depth (Figure 48-11A). When the tumor is ulcerated, the starting point of measurement is at the base of the ulcer instead (Figure 48-11B). It should be noted in contrast previous AJCC staging (7th edition), the current recommendation for measurement should be recorded to the nearest 0.1 mm instead of 0.01 mm. For example, a melanoma that is measured at 0.65 mm to 0.74 mm should be reported as 0.7 mm. Additionally, the presence of dermal mitotic figures no longer upstages the tumor from T1a to T1b. As for thin melanoma, T1b melanoma is now defined as 0.8 mm to 1.0 mm in thickness or any ulcerated melanoma <1 mm in thickness.[26]

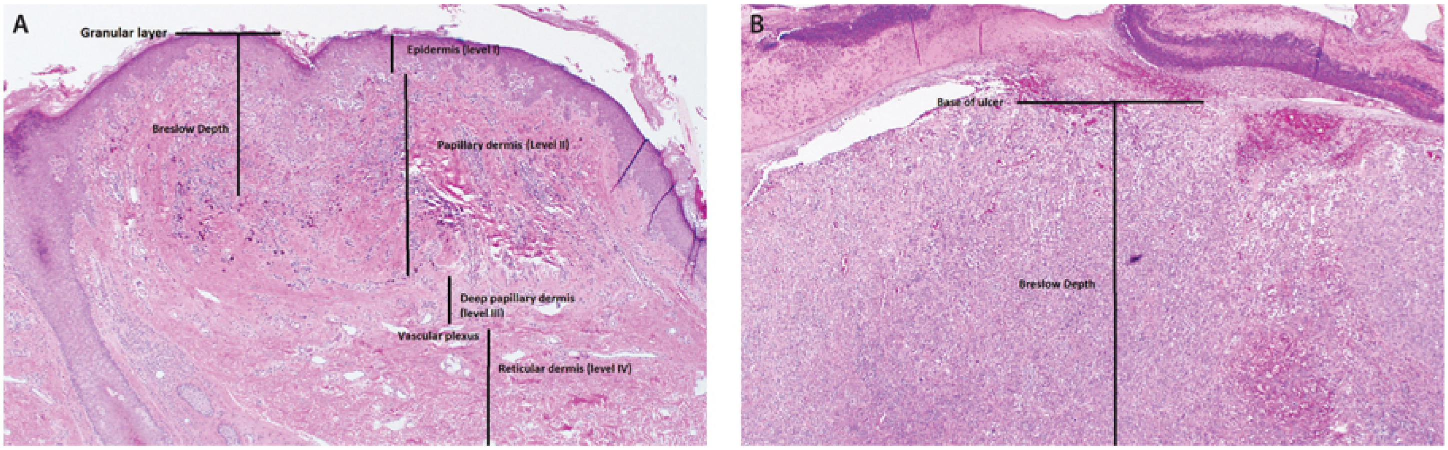

Figure 48-11. A, Example of a superficial spreading melanoma. Breslow depth is measured from the epidermal granular layer to the deepest dermal invasive focus with the most optimal perpendicular orientation. Clark levels are divided based on the level of involvement: epidermis (I), nonexpansile involvement of papillary dermis (II), expansile involvement of papillary dermis with extension to reticular dermal interface (III), and involvement of reticular dermis (IV). Distinction between papillary dermis and reticular dermis can be estimated based on the landmark vascular plexus in between and textural change of dermal collagens (more vertical alignment in papillary dermis and more horizontal in reticular dermis). Level V (subcutaneous) is not shown in the figure. B, Definition of ulceration in melanoma needs full-thickness ulcer with associated tumor cells infiltration and secondary inflammatory changes. Measurement of Breslow depth in an ulcerated melanoma begins from the base of the ulcer.

Another caveat in Breslow depth measurement is the presence of adnexal (hair follicle or sweat gland/duct) extension of tumor cells. These areas should not be confused with dermal invasive melanoma and should be avoided when performing Breslow depth measurement (Figure 48-12). On rare occasions, invasive melanoma could develop from the area of adnexal extension. In this rare case, the corresponding Breslow depth should be measured from the inner layer of the outer root sheath epithelium or inner luminal surface of sweat glands to the furthest extent of infiltration into the periadnexal dermis. Microsatellites, foci of neurotropism, or lymphovascular invasion (Figure 48-12) should not be included in tumor thickness measurements.

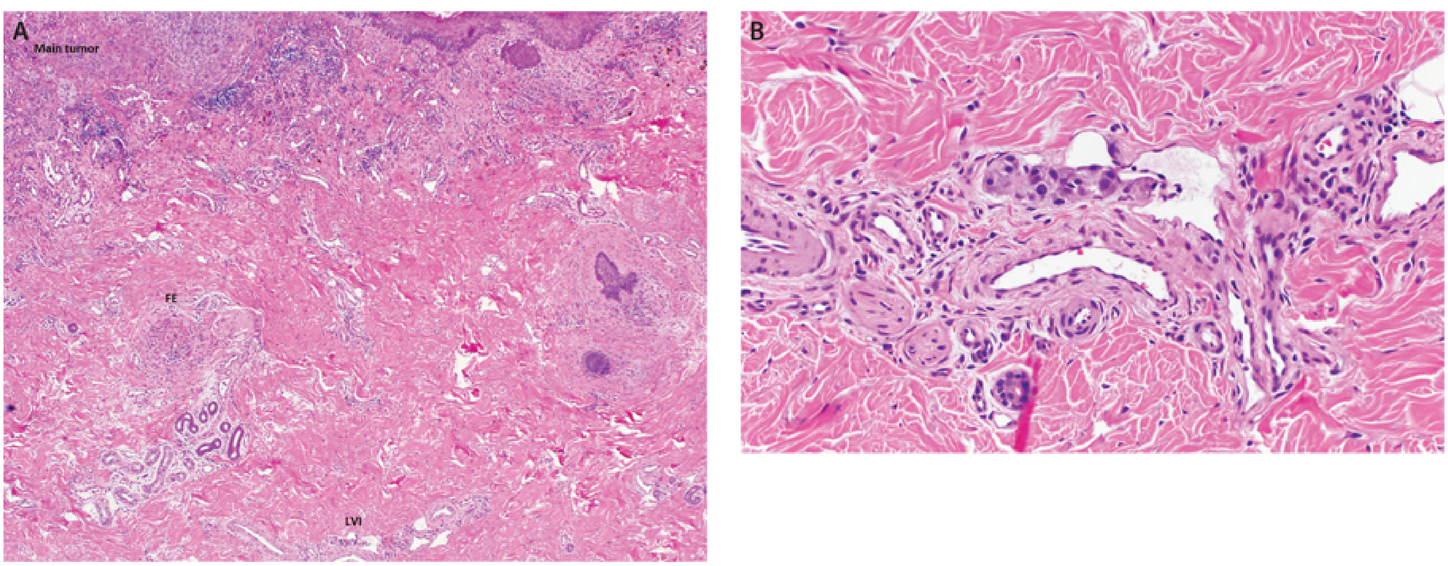

Figure 48-12. Melanoma follicular extension (FE) and lymphovascular invasion (LVI). A, Low-magnification view shows an overlying primary melanoma (main tumor), mid dermal FE, and deep dermal LVI. Breslow depth should not be measured to the level of FE or LVI. B, Higher magnification further illustrates the area of LVI in A.

Anatomic (Clark) levels have been used as an independent predictor of outcome. However, the definition of the Clark levels and how individual pathologists define them are more subjective in contrast to Breslow depth.

Therefore, Clark levels are no longer used for primary tumor staging purpose. Histologically, Clark levels are defined as follows: I-intraepidermal tumor only (ie, melanoma in situ); II-tumor present in but does not fill and expand the papillary dermis; III-tumor fills and expands the papillary dermis; IV-tumor invades into the reticular dermis; V-tumor invades into the subcutis.

Although pathologists typically do not have difficulty in defining level I, deep level IV, and level V lesions, variability exists in differentiating of level II from level III and level III from superficial level IV (Figure 48-11A). One can use superficial vascular plexus as a rough histologic landmark to distinguish between level III and level IV, while the distinction between level II and level III could be made based on several factors including quantitative evaluation of papillary dermal involvement (expansile vs nonexpansile), extension to the superficial portion of dermal vascular plexus, and/or dermal mitotic figures. In general, a tumor limited to Clark level II without any dermal mitotic figures should be considered radial growth phase only.

(c) Ulceration

Evaluation of ulceration in cutaneous melanoma has important clinical significance. Tumor ulceration is correlated with a poorer prognosis than nonulcerated melanomas.[26,33-35] Presence of tumor ulceration upstages the tumor from an “a” to a “b” category. However, there are pitfalls in accurately evaluating ulceration. Only full-thickness ulcer that is associated with tumor cells can be considered an ulcerated melanoma. Trauma or a prior procedure (biopsy)-associated wound changes should be especially excluded. Soft criteria indicative of ulceration include associated reactive changes such as fibrin and neutrophils, while the adjacent epidermis frequently shows reactive hyperplasia. These histologic changes can assist in determining the presence of true ulceration (Figure 48-11B). It should be noted that ulceration in melanoma in situ does not affect staging. Although studies have indicated the extent of ulceration has prognostic significance, this information has not been incorporated into the current tumor staging.

(d) Mitosis

Mitotic count has important role in predicting clinical behavior of melanoma.[26] However, pitfalls exist when mitoses are not evaluated properly.[36] Firstly, one should only count mitotic figures within the dermally invasive portion of the melanoma. Junctional or intraepidermal melanocytic mitosis should not be counted. Secondly, mitosis within intermixed inflammatory cells or endothelial cells in the stroma should be excluded. Counting of mitoses should focus on “hot spots,” the most mitotically active area in the dermis (assisted with low-magnification evaluation). Sometimes this is done by finding the first dermal melanocytic mitosis when mitotic activity is not prominent. The count is then extended to immediately adjacent nonoverlapping fields until an area of tissue corresponding to 1 mm^2 is assessed (Figure 48-13). The exact number count is preferred over a number range such as a statement of mitosis “$>0/mm^2$.” In addition, a statement of “$<1/mm^2$” should be avoided and expressed as “$0/mm^2$” instead. When the whole field of dermal invasive melanoma is less than 1 mm^2, the count can be expressed as if from 1-mm^2 field. Lastly, it should be noted an area of “1 mm^2” does not mean “1 high-power field or 10 high-power fields.” The area differs slightly depending on different types of microscopes. In general, an area of 1 mm^2 usually corresponds to between 4 to 5 high-power (400X) fields.

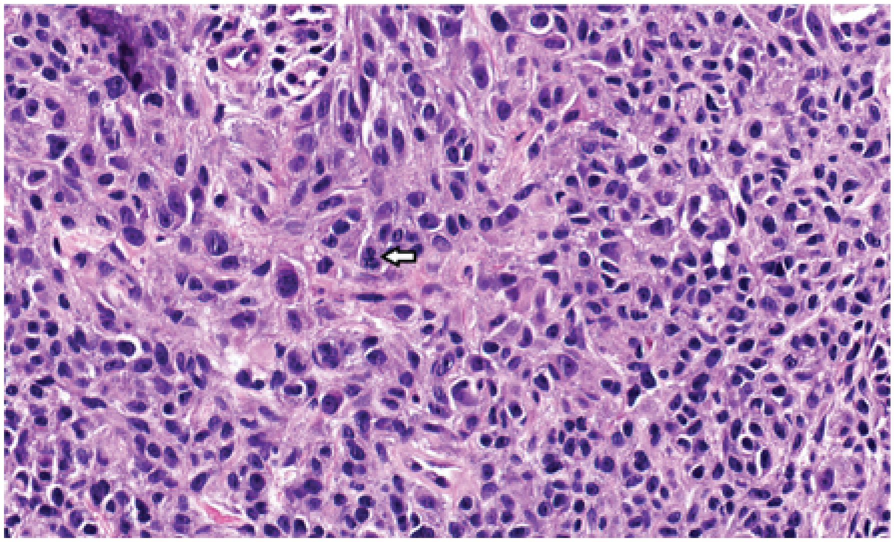

Figure 48-13. Mitotic count in melanoma should only be limited to dermal invasive component and begin with "hot-spot."

(e) Lymphovascular space invasion and neurotropism

Lymphovascular space invasion is infrequently encountered. However, it has strong association with risk of locoregional metastasis and poor long-term survival when present (Figure 48-12B). Although this is not required, utilization of immunohistochemical stains with vascular markers including D2-40, ERG, and CD31 can be helpful in determining the presence of lymphovascular space invasion.[37,38]

Neurotropism includes both perineural invasion and intraneural invasion.[26,27] This phenomenon is much more commonly seen in the setting of desmoplastic melanoma or melanoma with highly infiltrative growth pattern.[29] Occasionally the tumor can show neural transformation, which is also considered as neurotropism (Figure 48-10B). Recognition of neurotropism is important to determine the risk of local recurrence. However, the most common mistake in evaluating neurotropism is overinterpretation of trapped nerves within the main tumor, which is not an uncommon phenomenon. Therefore, identification of neurotropism should be performed at the infiltrative periphery of the tumor.

(f) Tumor regression

Tumor regression, specifically complete regression, is associated with a poor prognosis in melanoma.[26,27] However, correct recognition of regression is not always straightforward. The histologic features that are indicative of regression include lymphocytic inflammation, attenuation of the overlying epidermis, and nonlaminated dermal fibrosis with inflammatory cells, melanophages, and telangiectasia. These features are best evaluated in the setting of immediately adjacent melanoma to confirm they truly represent a tumor-regression process (Figure 48-14). Controversy exists in regard to the clinical significance of partial regression. Therefore, only complete tumor regression should be recorded in the staging report.

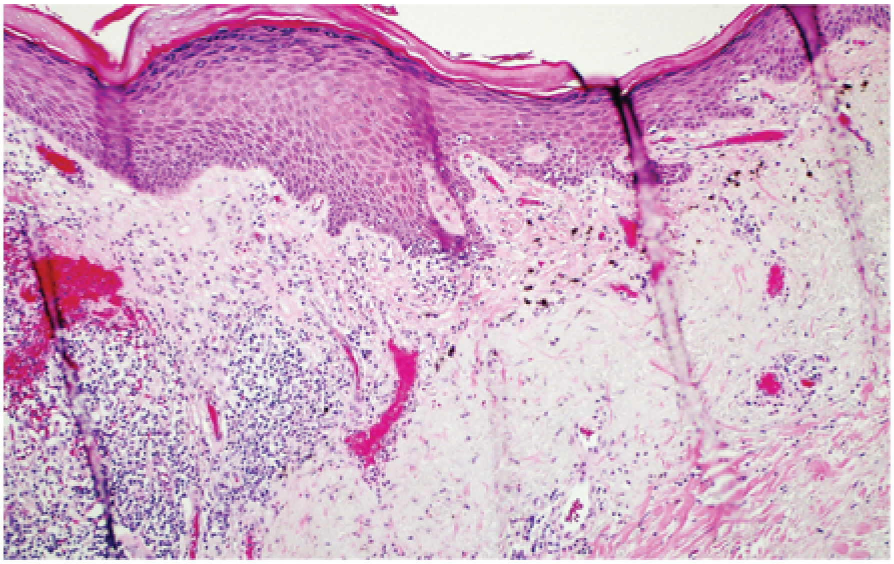

Figure 48-14. Melanoma tumor regression. Area immediately adjacent to a melanoma (left, not shown) with lymphocytic inflammation, nonlaminated dermal fibrosis, melanophages, and telangiectasia without any residual melanoma cells, consistent with complete regression.

(g) Tumor-infiltrating lymphocytes

A paucity of tumor-infiltrating lymphocytes (TILs) is an adverse prognostic factor for cutaneous melanoma.[26] In addition, the presence or absence of TILs may be an important factor in predicting response to immune checkpoint inhibitor treatment. Assessment of tumor-infiltrating lymphocytes needs to follow some strict criteria.[26] Brisk TILs can be seen in two patterns: (1) TILs diffusely permeate through the invasive tumor and (2) TILs surround the entire base of the invasive tumor (Figure 48-15). When there are TILs interacting with partial or focal invasive tumors, this phenomenon is considered as nonbrisk (Figure 48-15). When there is complete lack of lymphocytes or there are only lymphocytes that do not interact with tumor cells, TILs should be recorded as absent.

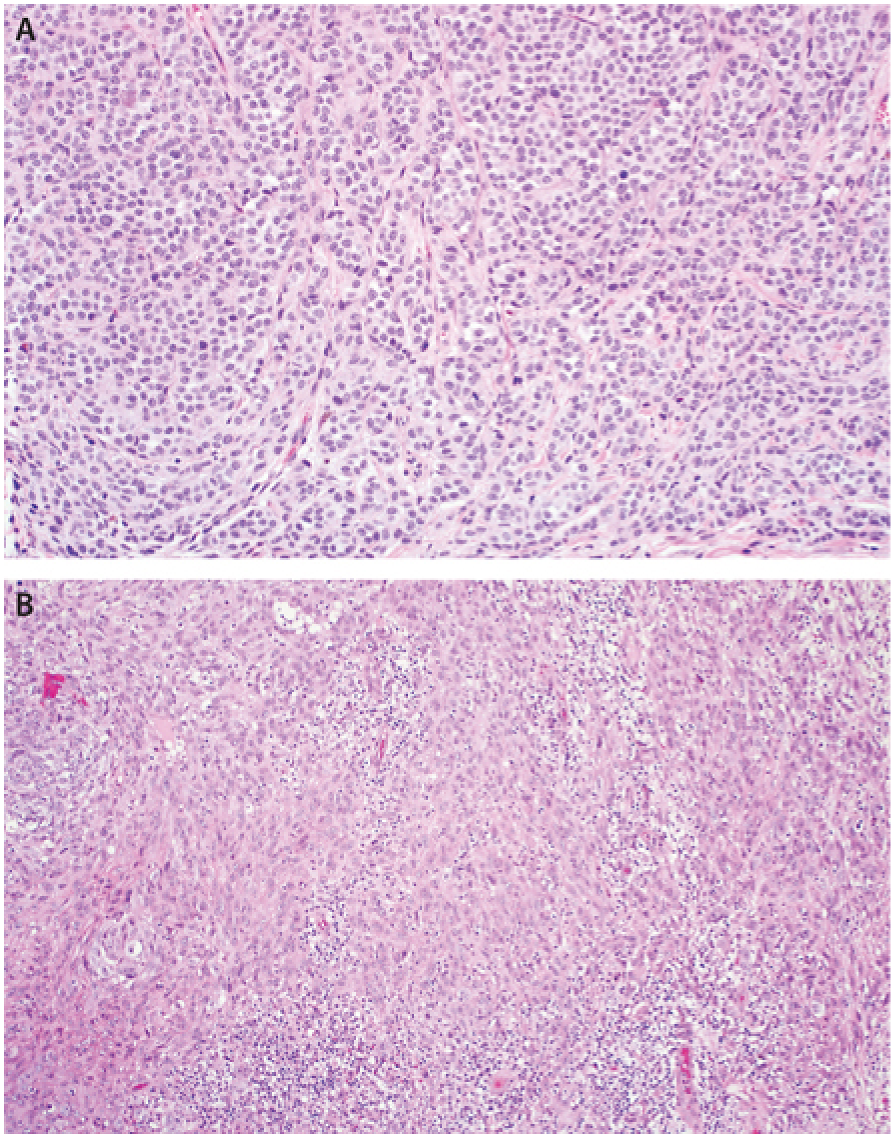

Figure 48-15. Melanoma tumor infiltrating lymphocytes. A, Nonbrisk (rare scattered lymphocytes within tumor). versus B, Brisk (diffuse lymphocytic infiltrates surrounding and permeating into tumor).

(h) Microsatellites

Microsatellites are a very important prognostic factor and should be accurately documented when observed.[26] A microsatellites means the presence of a microscopic cutaneous metastasis, which is either adjacent to or deep to a primary. When it is determined that a microsatellite is present, the tumor is considered locally metastatic and will be staged as at least N1c category. Therefore, accurate recognition of microsatellites is of critical clinical significance. This is usually done during pathologic examination of the primary melanoma; therefore, the pathologist has the primary responsibility in identifying microsatellites.[26]

It is a pitfall to miss such a microsatellite or to overcall it. The pathologist needs to be alert to such a discontinuous focus, which could be very small and easy to miss, and may need to perform deeper sectioning to determine if this focus is indeed discontinuous from the main tumor and showing no connection with dermal adnexal structures. In addition, the discontinuous zone between the main tumor and the separate tumor nodule should be composed of normal tissue (Figure 48-16). Although in previous version of the AJCC staging guideline, a tumor nodule size of at least 0.05 mm (diameter) and tumor-free zone by normal tissue of at least 0.3 mm were recommended, they are no longer the required criteria in the most recent version.

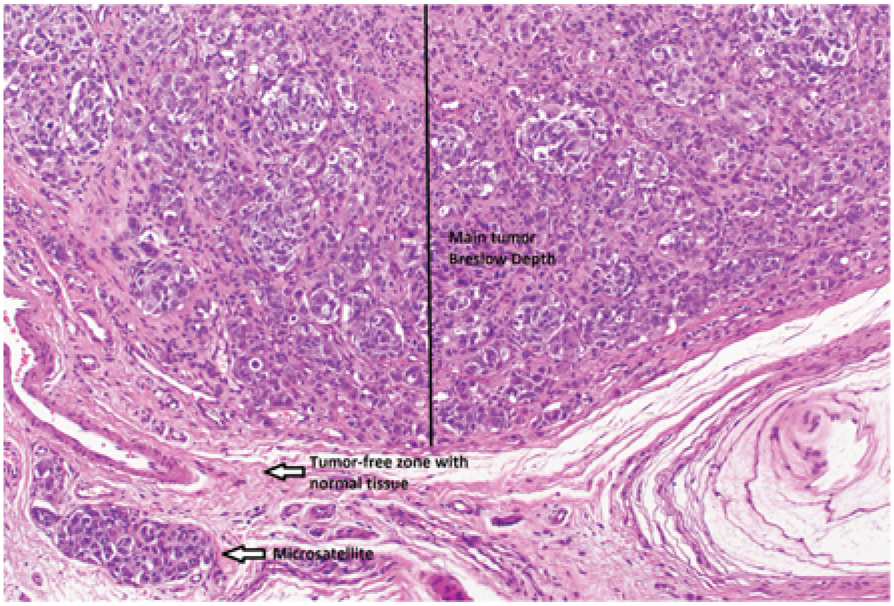

Figure 48-16. Melanoma microsatellite (deep portion view of a large invasive melanoma). The focus of microsatellite is separated from the main tumor by a tumor-free zone, which contains normal dermal connective tissue without inflammation, fibrosis, or melanosis. This zone is confirmed by extensive deeper sectioning of the tissue block. Recognition of the microsatellite in this case is critical to prevent erroneous measurement of Breslow depth as well as for accurate designation of tumor N stage (N1c if no positive regional lymph node, or N2c/N3c with additional positive regional lymph nodes).

(i) Sentinel lymph node

Sentinel lymph node (SLN) biopsy is frequently performed for melanoma with a thickness of 1 mm or greater or in cases of thinner melanoma with other high-risk factors. Handling of sentinel lymph nodes in surgical pathology is variable.[32,39,40] However, in general, multiple tissue levels by routine H&E-stained slides through serially sliced sentinel lymph nodes (bread-loafed) increases the sensitivity of detecting microscopic melanoma metastasis in contrast to simply bisecting the lymph node. In addition, a metastatic focus is very commonly only microscopic in a melanoma SLN biopsy. Therefore, immunohistochemical stains are routinely used in assisting detection of such microscopic tumor foci.[41,42] When the tumor cells are only detected by immunohistochemistry and are not visible on H&E, the finding is still considered as a positive lymph node. Currently, for a conventional melanoma, the recommended immunohistochemical stains are Mart1/Melan-A and HMB45, which are best used together. One diagnostic caveat is the presence of capsular/nodal nevus, which stains positively with Mart1/Melan-A while is mostly negative or weak for HMB45. On the contrary, HMB45 tends to stain positively in metastatic melanoma cells. Therefore, this staining pattern can be used in assisting the differential diagnosis between benign capsular/nodal nevus and metastatic melanoma (Figure 48-17).

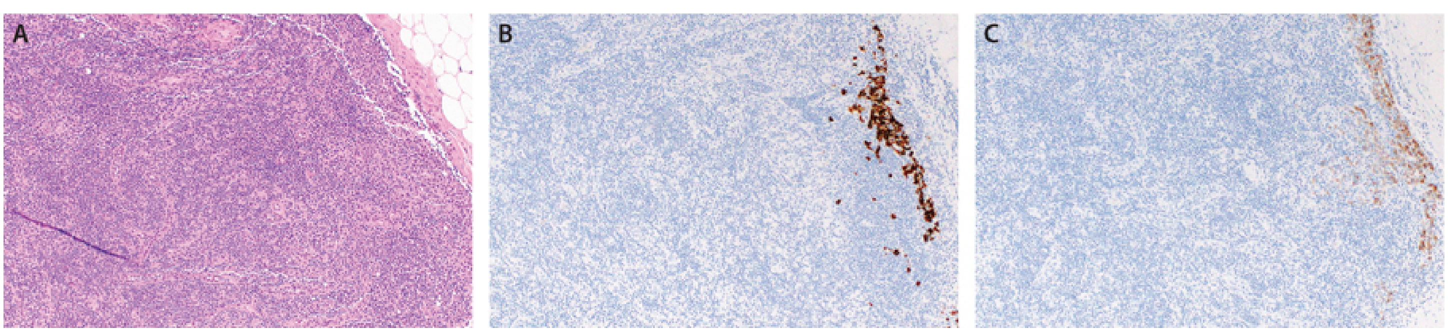

Figure 48-17. Melanoma sentinel lymph node, small focus of subcapsular to intraparenchymal melanocytes (A, H&E), Staining positively with Melan-A (B) and HMB45 (C). In contrast, benign nodal nevus is usually capsular and tends to stain negatively (or weakly) with HMB45.

(j) N and M stage

Although for the most part, the melanoma tumor N stage is intuitive, confusion may exist in incorporating the information of satellitosis/in-transit metastasis. Satellitosis by definition occurs within 2 cm of the primary tumor.[26] In-transit metastasis is defined as intralymphatic tumor in skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin (Figure 48-18). Presence of satellitosis/in-transit metastasis alone, including microsatellite and macrosatellite, qualifies for stage N1c, which is an important indicator of poor prognosis. Presence of satellitosis/in-transit metastasis with concurrent positive lymph nodes should be staged as N2c or N3c, depending on the number of positive regional lymph nodes.[26]

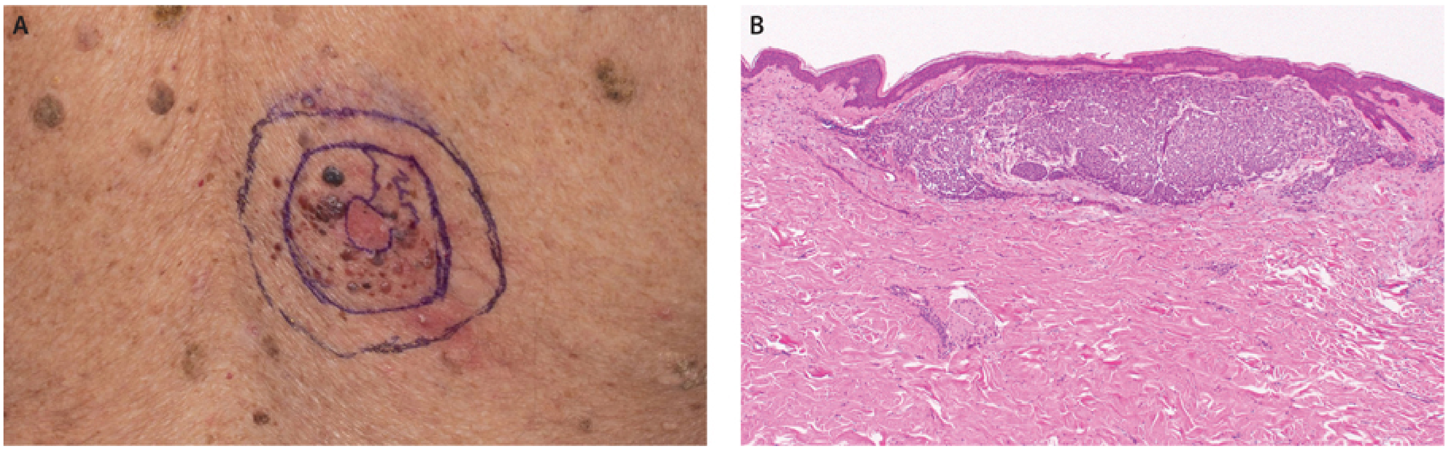

Figure 48-18. Melanoma-satellitosis/in-transit metastasis. A, Multiple pigmented papules and nodules near the prior biopsy site of the primary melanoma. B, H&E section of a representative lesion shows superficial dermal involvement by in-transit metastatic melanoma.

In addition, sometimes the distinction between N1a and N1b needs clinical correlation, with the former defined as a "clinically occult tumor-involved node" and the latter "clinically detected tumor-involved node."[26]

As for M stage, although pretreatment serum lactate dehydrogenase level is still considered as prognostically important and clinically relevant, this information does not need to be reported in the pathology report for M stage. It should be noted pM stage requires pathologic confirmation and documentation.[26]

(j) Final synoptic report

The common scenario for reporting cutaneous melanoma is an initial biopsy followed by a wide local excision. This has caused frequent confusion as for what to be reported in the final staging report, because it is not uncommon to observe no residual or minimal residual melanoma in the excision specimen. This problem is even more challenging when the initial biopsy and final excision are performed at different facilities. However, considering the purpose of synoptic report and with the best effort, the information of the initial biopsy and final excision should be combined into a final tumor staging report to make it useful for future clinical use. For example, a patient had a pT4b ulcerated nodular melanoma diagnosed by a punch biopsy, but 3 weeks later the excision did not show residual tumor. The final synoptic report should record the primary tumor as pT4b rather than pT0. The deepest Breslow depth and the highest pT stage should be used as the final depth and pT stage, no matter whether on the biopsy or the wide local excision.

D. Merkel cell carcinoma

Histologic evaluation of Merkel cell carcinoma for staging purpose has many similar aspects as melanoma, including the methods to record tumor thickness, mitotic count, and TILs, which all have important prognostic significance.[5,43-48] However, the primary T stage of Merkel cell carcinoma largely depends on clinical tumor size based on the current recommendation,[26] which is frequently overlooked. This can become even more challenging when the clinical measurement is not properly estimated at the time of biopsy. Another piece of critical information to document is the presence of deep structure involvement (bone, muscle, fascia, or cartilage), which make the tumor a pT4.[26,43] Pathologists should be alert to these findings. In addition, one pitfall

in evaluating sentinel lymph node for Merkel cell carcinoma is the presence of micrometastasis. The metastatic tumor cells often mimic background lymphocytes. Therefore, it is recommended to use immunohistochemical stains (such as AE1/AE3, Cam 5.2, CK20, synaptophysin, neurofilament—particularly a marker that was positive in the primary tumor) to assist SLN evaluation for Merkel cell carcinoma, many of which show a perinuclear dot-like staining pattern.[49,50]

E. Intraoperative tumor and margin assessment

In general, intraoperative tumor and margin assessment for skin tumors is only performed for curative excision. The most common procedures include Mohs micrographic surgery and standard surgical excision. The goal of Mohs micrographic surgery is to remove the tumor with clear margins by concomitant frozen section evaluation, with only the minimum amount of surrounding healthy tissue being removed. Therefore, this procedure is most commonly applied to treatment of nonmelanoma skin cancers at sensitive anatomic locations or tumors with irregular or infiltrative borders. During the procedure, the first step is often surgical debulking of the main tumor, followed by a thin layer of margin submitted for frozen section evaluation. The procedure is completed when a pathologic clear margin is achieved confirmed by frozen section evaluation. Mohs surgeons have training to be familiar with histomorphologic features of skin tumors under frozen section. When necessary, modified fast intraoperative immunohistochemical stains (such as keratin markers) can be applied to assist in margin evaluation. The pitfalls of Mohs surgery are the tumors with single cell infiltrative borders, discrete extension through perineural invasion, and spindle cell morphology.

As for standard surgical excision, the procedure is rarely used for diagnosis purpose, and the tumor usually has as an established histologic diagnosis from a prior biopsy procedure. Given the known tumor information, the margins can be evaluated either perpendicularly or en face, largely depending on the gross contour, histologic features, and anatomic location of the tumor. The advantage of perpendicular margin evaluation is that it can also provide accurate information regarding the geographic relationship between the tumor and margin, which is even more valuable when dealing with melanoma and Merkel cell carcinoma, where the margin distance is important to report[51] (Figure 48-19).

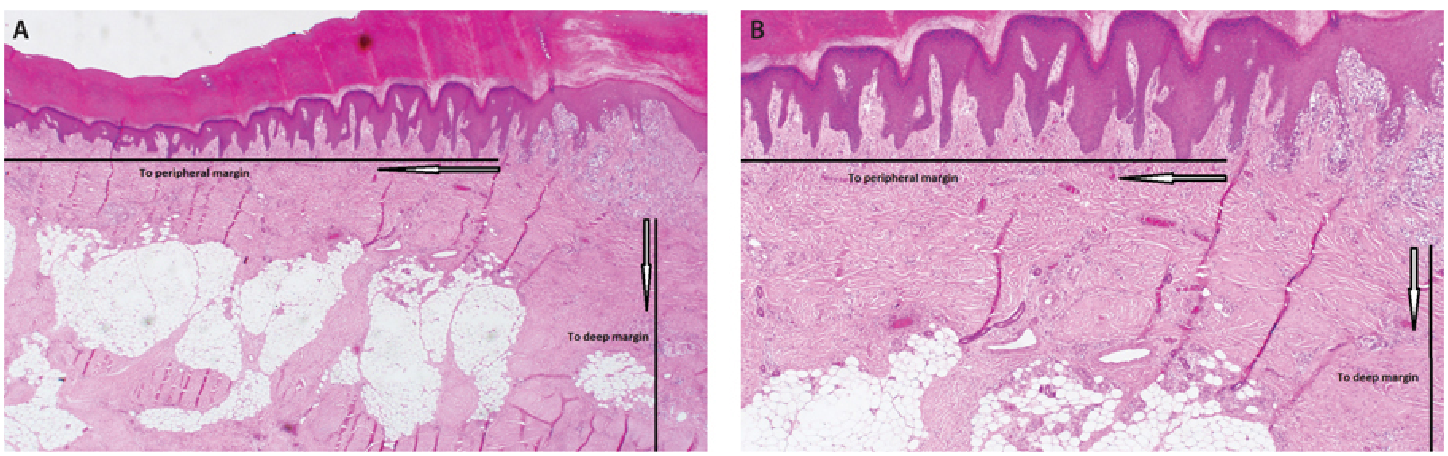

Figure 48-19. Melanoma excision margin evaluation. A (low magnification) and B (medium magnification) highlight the very peripheral edge of the tumor, and the horizontal arrowed lines indicate the direction of margin measurement to the closest peripheral surgical margin. The peripheral edge of the lesion frequently only contains melanoma in situ component as shown here. The vertical arrowed line indicates the measurement between the deepest invasion and the closest deep surgical margin. Most often a negative deep margin is sufficient for the surgical excision of the tumor in spite of the distance.

One important principle regarding surgical removal of cutaneous melanoma is to achieve an adequate surgical margin. In general, a 0.5-cm to 1-cm clinical margin is desired for melanoma in situ, while 1-cm to 2-cm clinical margin is optimal for an invasive melanoma. Microscopic evaluation of the margin is very important in assisting the surgeons to determine if the excision is adequate (Figure 48-19). It should be noted although pathologists should always measure the distance between the lesion (either in situ melanoma component or

invasive component) and the closest peripheral margin and report the microscopic distance, the final margin distance in fact should be primarily based on gross and clinical measurement by the surgeon. In addition, although it is ideal to report the distance between the invasive tumor and the closest deep margin, clinically there is no recommendation for how far the deep margin should be from the tumor, and a mere clear margin is usually deemed adequate. Again, the challenge for the evaluation of deep margin is the highly infiltrative melanoma, especially desmoplastic melanoma that can mimic background scar tissue histologically. If indicated, immunohistochemical stains (most commonly combination of S100, SOX10, and Melan-A) can be performed to assist margin evaluation.

VIII. What to include in the pathology report

The final pathology report should include important information listed by priority, although the reporting style may vary among practicing pathologists.

- Describe type of tumor: Is the neoplasm in situ or invasive?
- If invasive, include the histologic type and grade if applicable.
- What is the maximal depth of invasion?
- Is there perineural or lymphovascular invasion?
- What is the status of the margins?

An example report is provided below to demonstrate the necessary information to be included in a pathology report, and a synoptic template will be utilized.

FINAL DIAGNOSIS:

A. Skin, right back, wide local excision: Malignant melanoma, superficial spreading type, Breslow depth 2.4 mm, ulcerated with microsatellite, completely excised. See synoptic report.

B. Lymph nodes, right axillary sentinel, biopsy: 1 of 2 (1/2) lymph nodes positive for metastatic melanoma, largest tumor focus 1.1 mm in greatest dimension, no extranodal extension identified.

Synoptic report

The following information is a modification of the AJCC cancer staging protocol and CAP cancer staging checklist for malignant melanoma:

Procedure: Wide local excision and sentinel lymph node biopsy
Specimen Laterality: Right
Tumor Site: Right back skin
Macroscopic Satellite Nodule: Not identified
Histologic Type: Superficial spreading melanoma, invasive
Maximum Tumor (Breslow) Thickness: 2.4 mm
Ulceration: Present
Microsatellite(s): Present
Margins:
  Peripheral margin: Uninvolved by in situ or invasive melanoma
  Distance of invasive melanoma from closest peripheral margin: 12 mm
    Specify location: Right lateral
  Distance of melanoma in situ from closest peripheral margin: 9 mm
    Specify location: Right lateral
  Deep margin: Uninvolved by melanoma
Mitotic Rate: 5 /mm^2
Anatomic (Clark) Level: IV
Lymphovascular Invasion: Not identified
Neurotropism: Not identified
Tumor Infiltrating Lymphocytes: Present, brisk
Tumor Regression: Not identified
Regional Lymph Nodes

Total Number of Lymph Nodes Examined: 2
Number of Sentinel Nodes Examined: 2
Total Number of Lymph Nodes Involved: 1
Number of Sentinel Nodes Involved: 1
Size of Largest Metastatic Deposit: 1.1 mm
Size of Largest Metastatic Deposit in Sentinel Lymph Node: 1.1 mm
Extranodal Extension: Not identified.
Matted Nodes: Not identified
Pathologic Stage Classification (pTNM, AJCC 8th Edition)
TNM Descriptors: Not applicable
Primary Tumor: pT3b
Regional Lymph Nodes: pN2c
Distant Metastasis (pM): Not applicable

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49. Soft Tissue

Shi Wei, MD, PhD; Marilyn M. Bui, MD, PhD

Introduction

This chapter focuses on the specimens from surgical resections performed for primary malignant soft tissue tumors, including designated intralesional resection, marginal resection, wide resection, and radical resection. Evaluation of tumor type, histologic grade, margins, and pathologic stage are the key components of pathologic evaluation. In addition, neoadjuvant radiotherapy (RT) and chemotherapy have been increasingly used for large, high-grade, extremity soft tissue sarcomas to treat metastatic disease earlier, sterilize margins to perform margin-negative (R0) surgery, and limit loss of function after wide surgical excision, with the ultimate aim of improving patient survival. Thus, the evaluation of treatment effect is crucial in providing prognostic and predictive information.

Key points

- Prior to grossing, review the patient's pertinent history, including the radiology report, previous biopsy pathology report, and medical/surgical interventions such as surgical resection, radiotherapy, and chemotherapy, if any.
- Review the surgeon's operative procedure note, if available.
- Review the surgeon's instruction on the requisition form for specimen orientation (usually indicated by suture or clips) or other specific instructions, if any.
- For complex specimens such as ambiguous orientation, unusual gross appearance, or those that might be difficult to interpret/reconstruct once sectioned, inform the pathologist who will be ultimately responsible for the specimen. Communication with the surgical team is always useful for any query regarding the specimen.
- Obtaining a cross-sectional photograph with at least one patient identifier (eg, pathology accession number) is always helpful for documentation purposes and educational aide (such as tumor board), and is required in many institutions/laboratories.
- Specimens resected after neoadjuvant therapy require submission of representative tumor bed and respective margins even in the absence of grossly viable residual tumor. In fact, macroscopic assessment of posttreatment residual tumor is challenging and often impossible.

I. Indications for resection of soft tissue tumors

Primary malignant soft tissue tumors warrant limb-sparing resection or, rarely, amputation. Large-sized high-grade sarcomas that are sensitive for chemotherapy are typically subject to neoadjuvant chemotherapy in order to treat any early metastasis and sterilize margins to perform R0 resection. Neoadjuvant radiotherapy has been used in extremity sarcomas where upfront limb-conserving surgery is deemed difficult. If shrinkage of the sarcoma could facilitate conservative surgery, then radiotherapy may be utilized. Early surgery with wide negative margin is typically applied to the sarcomas that have poor response to neoadjuvant therapy. Thus, comprehensive evaluation of the pathologic materials obtained from the biopsy is crucial in providing accurate diagnosis to guide the subsequent treatment decision making.

Examples of intralesional resection include partial debulking or curettage. These procedures may leave macroscopic or microscopic tumor behind, thus staging is not always applicable. Marginal resection refers to removing the tumor (and its pseudo capsule, if present) with a relatively small amount of surrounding tissue. The margin is grossly negative for tumor; however, it may be positive by microscopic examination. The latter renders a procedure intralesional resection. Note that an "excisional" biopsy may effectively accomplish the same outcome as a marginal resection. With a wide resection, the tumor is removed with a cuff of surrounding normal tissue, but not an entire muscle group, compartment, or bone, thus is also known as an

intracompartmental resection. Lastly, radical resection is to remove an entire soft tissue compartment (eg, anterior compartment of the thigh) or bone, or the excision of the adjacent muscle groups if the tumor is extracompartmental.

Therefore, perceiving an adequate clinical history is necessary (and must be provided by submitting physician) before gross examination of a specimen. Pertinent clinical history includes (but is not limited to) prior diagnoses, prior or current treatment, and the type of specimen (as previously mentioned).

II. What do we expect to see in the soft tissue resection specimen?

Histologic type

Soft tissue sarcomas are largely classified into adipocytic, fibroblastic/myofibroblastic, so-called fibrohistiocytic, smooth muscle, pericytic (perivascular), skeletal, vascular, peripheral nerve, gastrointestinal stromal tumor, chondro-osseous, tumors of uncertain differentiation, and undifferentiated small round cell sarcomas of bone and soft tissue according to the current World Health Organization classification of tumors of soft tissue and bone.[1]

It is important to note that molecular and cytogenetic analyses play a crucial role in the classification of soft tissue tumors. Pathologists should take advantage of the opportunity of close-to-fresh tissue so the tissue is appropriately triaged for ancillary testing to facilitate a definitive diagnosis. In addition, some treatment protocols require fresh tissue for correlative studies. Thus, it is critical to snap freeze a small portion of tumoral tissue, whenever possible, for potential future use.

Histologic grade

Histologic grading is the most important prognostic factor and the best indicator of metastatic outcome in soft tissue sarcomas.[2] The most commonly used sarcoma grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and the National Cancer Institute (NCI) systems. Both are three-tier grading systems based on differentiation, tumor necrosis, and mitotic activity.[2,3] The FNCLCC system (Table 49-1) may be slightly better in predicting distant metastasis than the NCI system[4] and thus is adopted by the 8th edition of the *AJCC Cancer Staging Manual*.[5] It is important to note that accurate grading requires an adequate sample of tissue, which is not always available from fine-needle aspiration or core needle biopsy specimens or in tumors following neoadjuvant radiation or chemotherapy.

Table 49-1. French Federation of Cancer Centers Sarcoma Group (FNCLCC) Grading System[6]

Parameters	Definition
Differentiation	Score 1: Sarcomas closely resembling normal, adult mesenchymal tissue and potentially difficult to distinguish from the counterpart benign tumor (eg, well-differentiated liposarcoma, well-differentiated leiomyosarcoma)
	Score 2: Sarcomas for which histologic typing is certain (eg, myxoid liposarcoma, myxofibrosarcoma)
	Score 3: Embryonal sarcomas and undifferentiated sarcomas, synovial sarcomas and sarcomas of doubtful tumor type
Mitotic count	Score 1: 0-9 mitoses per 10 HPF*
	Score 2: 10-19 mitoses per 10 HPF
	Score 3: ≥20 mitoses per 10 HPF
Tumor necrosis	Score 1: No necrosis
	Score 2: <50% tumor necrosis
	Score 3: ≥50% tumor necrosis
Histologic grade	Grade 1: Total score 2, 3
	Grade 2: Total score 4, 5
	Grade 3: Total score 6, 7, 8

* HPF: high-power field (0.1734 mm^2), X40 objective, most mitotically active area, away from areas of necrosis.

III. Typical macroscopic appearance

Examples of some common sarcomas are illustrated in Figures 49-1 through 49-8 including high-grade sarcoma with rhabdomyosarcomatous differentiation (Figure 49-1), high-grade leiomyosarcoma (Figure 49-2), high grade undifferentiated pleomorphic sarcoma (Figure 49-3), metastatic gastrointestinal stromal tumor (Figure 49-4), extraskeletal osteosarcoma (Figure 49-5), high-grade fibroblastic sarcoma (Figure 49-6), a heterogeneous high grade sarcoma (Figure 49-7), and Ewing sarcoma (Figure 49-8).

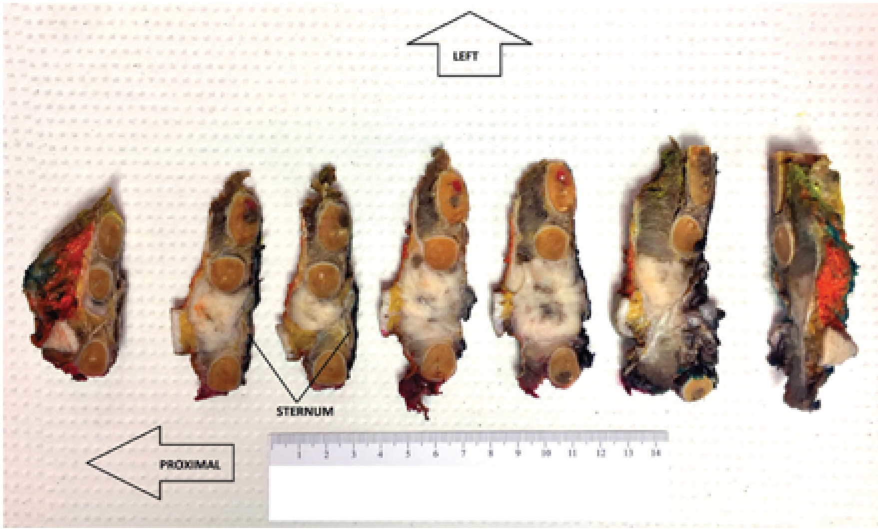

Figure 49-1. Dissection of an anterior chest wall high-grade sarcoma with rhabdomyosarcomatous differentation. Serially sectioning of the tumor demonstrates its relationship to adjacent anatomic structures (sternum and ribs) and margins as desginated by different inks. The tumor is tan-white and firm.

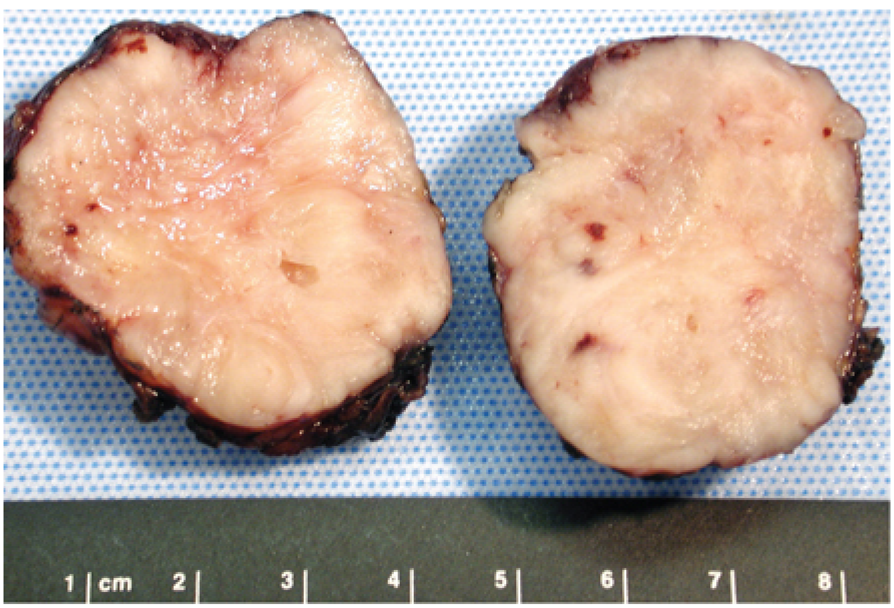

Figure 49-2. Cross-sections of retroperitoneal mass. The tumor is grossly present at undesignated inked margins. Histologic sections demonstated a high-grade leiomyosarcoma.

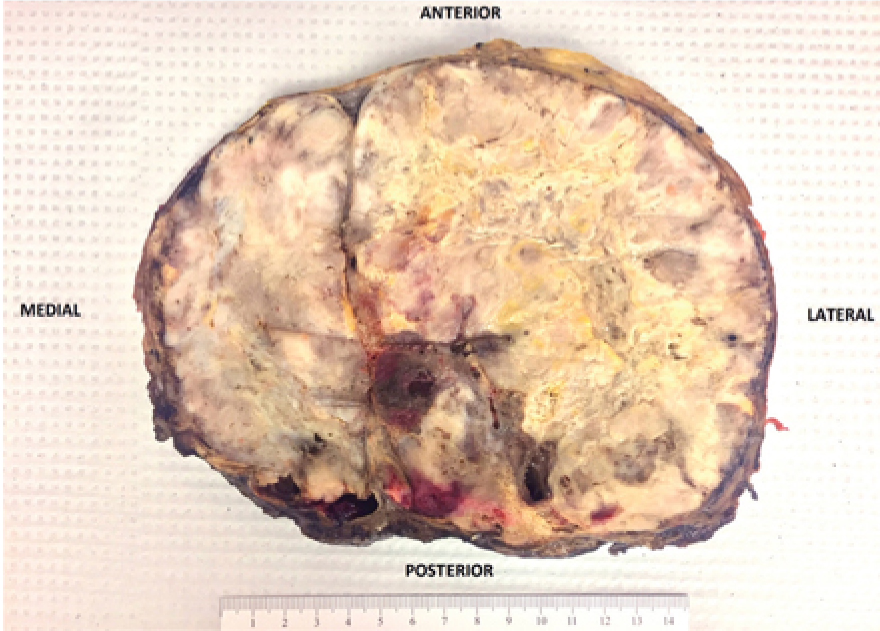

Figure 49-3. Cross-section of a large, right thigh, high-grade undifferentiated pleomorphic sarcoma demonstrates extensive necrosis. The tumor is close but not grossly present at inked margins.

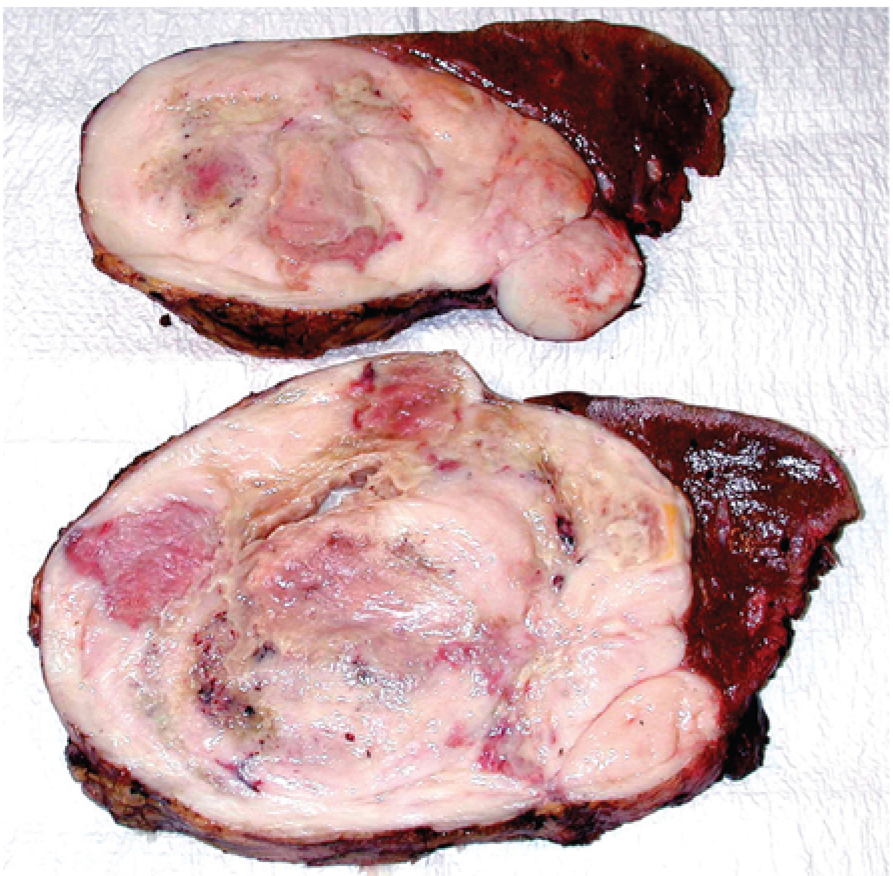

Figure 49-4. Cross-sections of metastatic gastrointestinal tumor to the liver. The resection margin of the liver is inked and the distance of tumor to the margin should be documented. The cut surface is tan and firm with hemorrhagic, necrotic, and cystic change.

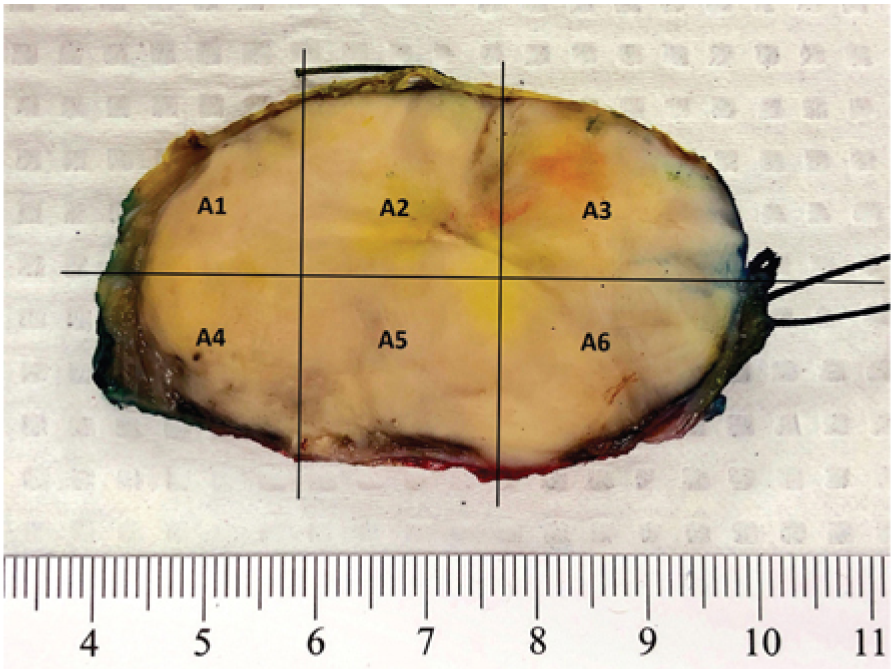

Figure 49-5. Marginal resetion of recurrent left leg extraskeletal osteosarcoma. The cut surface is firm with bone formation. A slice of tumor is entirely submitted with mapping of histologic sections.

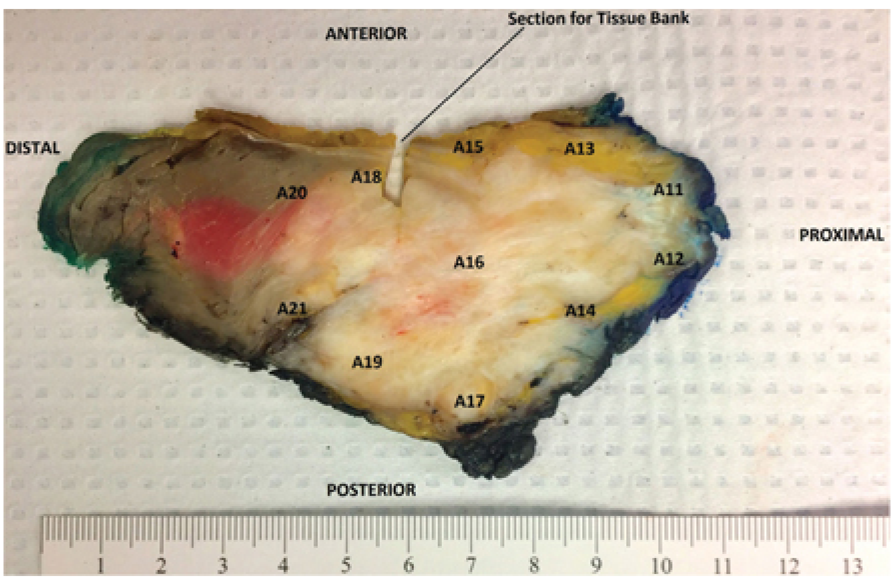

Figure 49-6. Cross-section of a high-grade fibroblastic sarcoma of a right medial thigh invading the skeletal muscle. The cut surface demonstrates a tan-white, firm, and homogeneous consistency. Representative sections with mapping of histologic sections. One section was submitted for tissue bank.

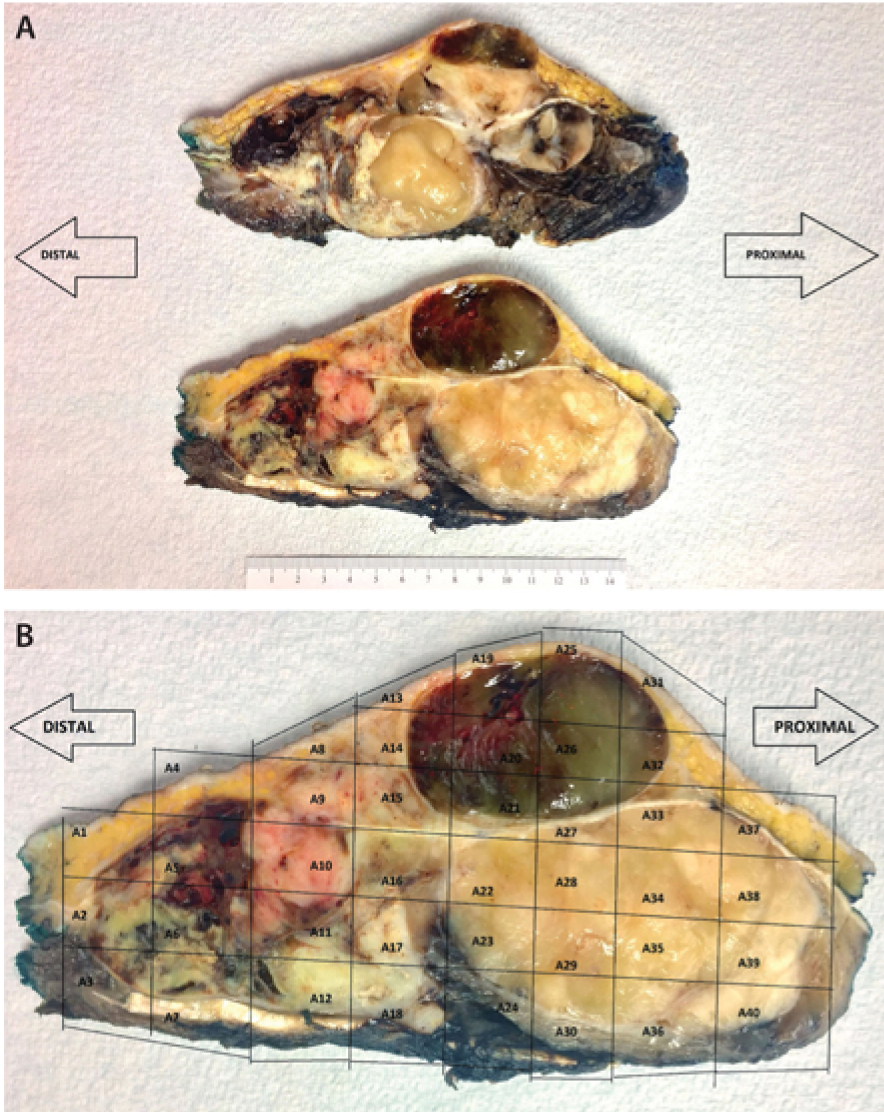

Figure 49-7. Cross-sections of a large, soft tissue, high-grade sarcoma of a left lower leg with heterogeneous-appearing cut surface (A). An entire slice is submitted with mapping of histologic sections (B). The tumor contains high-grade myxoid, spindle, pleomorphic, and osteosarcoma components. Low-grade myxofibosarcoma, hemorrage, and necrosis are also seen.

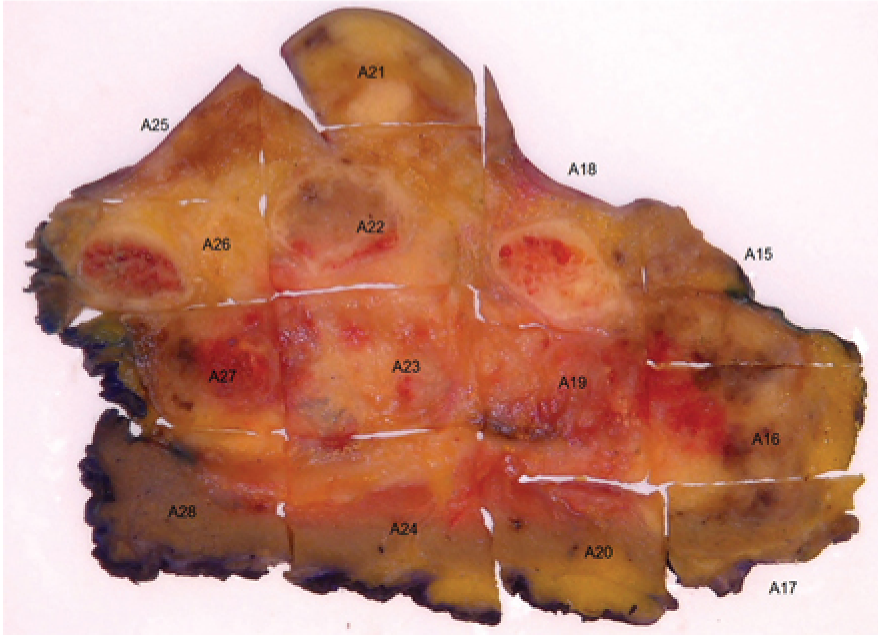

Figure 49-8. Cross-section of a chest wall soft tissue Ewing sarcoma involving ribs after neoajuvant chemotherapy. A slab of tumor is entirely submitted with mapping of histologic sections. Tumor necrosis is noted representing therapy change. The tumor is white-tan color and soft.

IV. Dissection techniques: step-by-step description

Each specimen should be approached with specific plans in mind based on the type of specimen. For example, resection of retroperitoneal sarcoma may be accompanied by adherent or entrapped other organs such as kidney or segment of colon, whereas excision of soft tissue sarcoma of the extremity may include fascial compartments. Thus, identification of all anatomic structures present is essential as the first step of gross examination. A step-by-step approach is described as follows.

1. Orientation markers (eg, sutures) must be identified, as they are the “landmarks” for subsequent reporting of the margins. If a procedure is unclear or if there is conflicting information about orientation, the clinician should be contacted before proceeding. Review of operative notes, if available, may be of help at times in this regard.

2. Measurement of the specimen dimensions utilizing international units (typically centimeters with one decimal point) should be taken on intact specimens prior to dissection. Measurement of tumor dimensions should be performed after dissection for large resections.

3. The tissue edges (margins) should be inked, aiding in the identification and correct orientation of the tissue pieces during embedding and histologic examination. The ink code should be provided in the gross description.[5] The surgical margins are usually designated by sutures or staples. The sutures and staples should be carefully removed prior to inking. A note in the gross description should be included indicating that a new margin underlying the staple line is taken. However, for large complicated specimens with grossly negative margins, inking may be delayed until the closest areas of the tumor to the margins are identified after dissection, so that the anatomic landmarks are not obscured by the ink. Care must be taken not to artificially introduce ink into tissue that is not present at the margin. The following are some inking tips for beginners.

a. Blot specimen dry with a paper towel or gauze before inking. Pat ink on surface with a sponge, gauze, or cotton applicator. Do not pour ink over the specimen.

b. Unoriented specimens should be inked one color (eg, black or blue), while oriented specimens with margins should be inked multiple colors. The application color and location will typically be dictated into the gross description. Change gloves if necessary to avoid introducing ink into the interior of the specimen.

c. Apply ink fixative to prevent it from dissolving in formalin. Section the specimen after thoroughly drying with paper towel or gauze.

4. The specimen should be completely dissected and serially sectioned while keeping the orientation in mind. The specimen orientation should remain recognizable even after a thorough dissection (Figures 49-1 through 49-4). Once the pathologic process (ie, tumor) is identified, the gross examintion/description is directed towards following key elements:

a. Size (nearest cm)

b. Consistency (ie, firm, hard, rubbery, gelatinous, etc)

c. Growth pattern (ie, well-circumscribed, infiltrative, etc)

d. Necrosis (and % if present)

e. Relationship with adjacent structures (ie, invasion into adjacent organ/compartment/vasculature)

f. Distance from resection margins

g. Previous biopsy cavity (if present)

h. Identification of regional lymph nodes, if applicable

5. Histologic sections are taken to best demonstrate the pathologic process. They should not be simply random sections. Small tumors can be entirely submitted, while larger lesions may be representatively submitted (one section per centimeter of tumor). The margins should be taken at the sites most likely to show tumor at (or closest to) the margin. When the tumor demonstrates a heterogeneous gross apperance, sections from different-appearing tumor must be taken. For assessment of treatment response after neoadjuvant therapy, submitting an entire slice of tumor is required. Spatial mapping of histologic sections is crucial in order to provide accurate information and to avoid errors (Figures 49-6 and 49-7). The section code (also known as block summary) should be provided in the gross description.[5]

6. Sampling of the tumor to access chemotherapy response is needed for some specimen types (eg, Ewing sarcoma). This is typically performed by taking one full cross-sectional slab of tumor at its greatest cross-sectional area, along with appropriate specimen photograph and mapping (Figure 49-8). The percentage of viable tumor estimation by microscopic examination is calculated by the sum of all areas of necrosis divided by the total cross-sectional tumor which is sum of 100.

7. Given the increasingly utilized molecular genetic analysis in the diagnosis of soft tissue tumors, it is important to triage fresh tumor tissue for ancillary studies. While formalin-fixed paraffin-embedded tissue can be utilized for many molecular analyses, including fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), and next generation sequencing, fresh-frozen tissue remains ideal for most cytogenetic analyses, high-throughput genomic studies, and long-term storage for potential future studies (following institution's biospecimen repository protocols).

8. Some specimens require fixatives other than formalin. For example, gouty crystals are water soluble and thus should be submitted in alcohol. Lymphoma may rarely present as a soft tissue mass. Thus, when in doubt, a portion of lesional tissue can be submitted in Roswell Park Memorial Institute (RPMI) medium for flow cytometry analysis.

V. Gross description using paragraph system

Gross description is an esential component in the pathology report as it provides pertinent information to the sign-out pathologist as well as the treating physicians. The paragraph system is thought to be a superior method in this regard as it efficiently communicates pathologic information and provides a working model for medical profesionals-in-training.[5] The system is simple in its approach to gross pathology dictation, breaking down the body of the dictated report into at least five distinct paragraphs, including specimen elements, primary pathology, secondary pathology, inking code, and section code (also known as block summary). The following is such an example.

Sample gross description

The specimen is received fresh, labeled with the patient's name, medical record number, and "left posterior thigh sarcoma." The specimen was oriented as follows: long stitch = proximal; short = lateral; white = posterior. It consists of a 122.8-gram, oval, tan-brown fragment of rubbery tissue measuring 10.5 cm (proximal to distal) x

5.8 cm (medial to lateral) x 5.0 cm (anterior to posterior). The specimen is inked to maintain the orientation as follows:

Blue – Proximal margin
Green – Distal margin
Red – Medial margin
Yellow – Lateral margin
Black – Anterior margin
Orange – Posterior

The specimen is serially sectioned to reveal a well-circumscribed, homogeneous, tan-white, firm mass measuring 7.5 cm (proximal to distal) x 4.3 cm (anterior to posterior) x 4.1 (medial to lateral). The mass is 1.0 cm from the anterior inked margin, less than 0.1 cm from the posterior margin, 1.5 cm from the medial margin, 2.8 cm from the lateral margin, 2.5 cm from the proximal margin, and 0.3 cm from the distal margin. No tumor necrosis is grossly identified. Representative sections are submitted as follows:

A1-A2: Mass with anterior margin, perpendicular sections
A3-A4: Mass with posterior margin, perpendicular sections
A5-A6: Mass with proximal margin, perpendicular sections
A7-A8: Mass with distal margin, perpendicular sections
A9-A10: Mass with lateral margin, perpendicular sections
A11-A12: Mass with medial margin, perpendicular sections

VI. Common potential staging pitfalls and solutions

The most commonly used staging system in the United States is the American Joint Committee on Cancer (AJCC) cancer staging system. While tumor site and tumor size are essential parameters in the macroscopic examination, histologic type, histologic grade, mitotic rate, the extent of necrosis, regional lymph node, and distant metastasis are required elements in the College of American Pathologists (CAP) cancer protocols based on the *AJCC Cancer Staging Manual*.[6]

Pathologic stage classification

In the 8th edition of the *AJCC Cancer Staging Manual,* the anatomic site is integrated into the TNM stage classification of soft tissue sarcomas.[6] This is due to the fact that smaller and anatomically confined sarcomas are prognostically favorable than larger and more extensively involved sarcomas. Head and neck, trunk and extremities, abdomen and thoracic visceral organs, retroperitoneum, and orbit each have a separate pathologic tumor stage (pT) classification. As an example, the cutoffs for pT1 and pT2 are 2 cm for sarcomas of the head and neck including the orbit, 5 cm for those occurring in trunk/extremities/retroperitoneum, and whether or not organ-confined for abdominal and thoracic visceral tumors. Note that although size criteria currently vary by anatomic site, emphasis should be placed on providing accurate size measurements. Tumor size should be regarded as a continuous variable, with the centimeter cutoffs as arbitrary divisions. Regional lymph node status is categorized as pN0 or pN1 (presence of regional nodal metastasis regardless of the number of nodes involved). Distant metastasis (pM) is required to be recorded only if confirmed pathologically in the case.

Potential staging pitfalls

1. The pathologic stages (pT) of soft tissue sarcomas are largely based on the site and size of the tumor. Head and neck, trunk and extremities, abdomen and thoracic viscera, retroperitoneum, and orbit each have a separate and distinct TNM classification. This is because the anatomic site of the tumor influences clinical outcomes.
2. Hematologic malignancies are not staged using soft tissue tumor protocol.
3. The clinical stage is outside the scope of this book, thus will not be discussed in this chapter.

VII. What to include in the pathology report

A pathology report should be concise while providing pertinent information to the treating physicians. The essential elements include (but are not limited to) tumor type, histologic grade, tumor size, surgical margins, lymphovascular invasion (if any), and nodal status. Some of the more detailed information can be included in

the synoptic report. Pathologist's comments may be needed in some cases to provide supplemental information to the treating physicians or the pathologist(s) who may subsequently review the case over the course of patient care. The following is such an example.

Sample pathology report

Soft tissue, left posterior thigh mass, resection:

- Dedifferentiated liposarcoma, FNCLCC Grade 2.
- Tumor measures 7.5 cm in greatest dimension.
- Surgical margins free of tumor.
- Pathologic stage: pT2 NX.
- See comment and synoptic report.

Pathologist comment:

A well-differentiated liposarcoma is identified. There is an abrupt transition between the well-differenitated and dedifferentiated components; the latter is composed of predominantly spindle cells with moderate nuclear pleomorphism in the background of collagenous stroma.

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2. Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med.* 2006;130(10):1448-1453.
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5. Dayton AS, Ro JY, Schwartz MR, Ayala AG, Raymond AK. Raymond's Paragraph System: an alternative format for the organization of gross pathology reports and its implementation in an academic teaching hospital. *Arch Pathol Lab Med.* 2009;133(2):298-302.
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50. Bone

Marilyn M. Bui, MD, PhD; Yaxia Zhang, MD, PhD; Evita Henderson-Jackson, MD

Introduction

This chapter focuses on the limb-sparing resection or amputation specimens which are indicated for primary malignant bone tumors. Evaluation of tumor type, grade, margin, and stage are the key components of pathologic evaluation. In addition, common high-grade primary bone sarcoma specimens, such as osteosarcoma and Ewing sarcoma, typically undergo neoadjuvant chemotherapy. The evaluation of treatment effect is crucial in providing prognostic and predictive information. Curettage samples for treating benign bone tumors and en bloc excision for locally aggressive tumors are outside the scope of this chapter.

Key points

- Before grossing specimen, check patient's history, reason for surgery, and previous cases. (Note: review patient chart for prior biopsy/excision/resection specimens, chemotherapy, and/or radiation treatment.)
- Review patient's radiographic reports prior to surgery (x-ray, computed tomography [CT], magnetic resonance imaging [MRI], ultrasound, etc). (Note: correlate tumor size, orientation, site of involvement, and/or treatment effect in reports.)
- If available, review the surgeon's operative procedure note.
- In case there is a complex specimen with ambiguous orientation or unusual gross appearance, or the specimen will be difficult to interpret/reconstruct once sectioned, inform the pathologist that will be receiving the case to review the specimen. Communicating with the surgical team for orientation is also useful.
- All specimens oriented and unoriented with a mass/lesion require an accompanying cross-sectional photomicrograph. (Note: on photomicrograph, indicate inked margins [proximal, distal, etc] when available and microscopic sections.)
- The surgical resection specimens with neoadjuvant therapy require a representative cross-section of the tumor submitted for evaluation of therapy changes. A photomicrograph of this section marking the correspondent block numbers (including medical record number, surgical number, surgical date, and patient's name) will be kept as a part of the medical record and as a part of the surgical pathology report. In addition, surgical margins and random sections of the tumor should also be submitted for histologic examination.
- With current processing techniques, most orthopedic specimens should be delayed only one extra day for decalcification. Longer delay usually means that the submitted sections were not adequately fixed prior to decalcification or were too big or too thick. Use a band saw to trim bone samples so that they easily fit into a plastic cassette. When in doubt, work with histotechnologists and pathologist assistants for a customized solution.

I. Indications for bone resection

Primary malignant bone tumors warrant limb-sparing resection or amputation. High-grade sarcomas that are sensitive to chemotherapy are typically subject to neoadjuvant chemotherapy. Pathologic fracture does not necessarily warrant amputation in the case of chemosensitive sarcomas. Neoadjuvant chemotherapy with a good response will contract the fracture hematoma and allow subsequent resection of the tumor and involved soft tissue. For sarcomas that have poor response to neoadjuvant chemotherapy, early surgery with wide negative margin can be considered. For chemoresistant sarcomas, amputation is warranted. Comprehensive pathologic evaluation provides critical diagnostic, prognostic, and predictive information to guide patient management.

II. What do we expect to see in a bone resection specimen macroscopically and microscopically?

Histologic type

Osteosarcoma, chondrosarcoma, Ewing sarcoma, chordoma, and undifferentiated pleomorphic sarcoma are common primary bone sarcomas.[1] Data from 3000 primary malignant bone tumors seen at the Royal Orthopedic Hospital in Birmingham, England, show that osteosarcoma involves mainly the knee (66%), hip and pelvis (15%), and shoulder girdle (10%). Conventional osteosarcoma is the most common histologic type that mainly occurs in patients 10 to 14 years of age, with 30% occurring after the age of 40. Chondrosarcoma involves mainly the hip and pelvis (48%), knee (17%), and shoulder girdle (15%). Conventional chondrosarcoma is the most common histologic type that occurs in patients older than 50 years of age. The common locations of Ewing sarcoma are the hip and pelvis (44%), knee (22%), lower leg (13%), and shoulder girdle (11%). The typical Ewing sarcoma patients are Caucasians younger than 20 years of age. Chordoma typically involves the base of skull, the vertebral bodies, and the sacrococcygeal bone in patients in their 50s to 70s. Undifferentiated pleomorphic sarcoma represents less than 2% of primary bone malignancies. It mainly involves the knee (41%) and hip and pelvis (29%) in patients of older age. The data from Mayo Clinic and Beijing Ji Shui Tan Hospital based on comparison of 10,165 and 9200 patients treated at these hospitals, most malignant primary bone tumors involve the femur (25% vs 42.3%), tibia (14.1 vs 19.6%), pelvis (9.6% vs 11.1%), humerus (9.5% vs 9%), and sacrum (8.9% vs 5.7%).[2] In addition to the above sarcomas of bone, spindle cell sarcoma, hemangioendothelioma, angiosarcoma, fibrosarcoma/myxofibrosarcoma, and adamantinoma are other primary sarcomas that may arise in the bone.[3] For a complete listing of the bone sarcomas, please refer to the most recent edition of the World Health Organization classification of tumors of soft tissue and bone.[1]

Tumor grade

Grade 1 sarcomas have a better prognosis than higher grade sarcomas. Grade 1 (well-differentiated) bone sarcomas include parosteal osteosarcoma, grade 1 chondrosarcoma, clear cell chondrosarcoma, and low-grade osteosarcoma. Grade 2 (moderately differentiated) bone sarcomas are periosteal osteosarcoma, grade 2 chondrosarcoma, classic adamantinoma, and chordoma. Grade 3 (poorly differentiated) bone sarcomas are high-grade conventional osteosarcoma, telangiectatic osteosarcoma, small cell osteosarcoma, high-grade surface osteosarcoma, undifferentiated pleomorphic sarcoma, Ewing sarcoma, grade 3 chondrosarcoma, dedifferentiated chondrosarcoma, mesenchymal chondrosarcoma, dedifferentiated chordoma, and malignant giant cell tumor of bone. In the 8th edition of *AJCC Cancer Staging Manual* of bone, there are the following changes: (1) stage III is reserved for grade 2 and grade 3 sarcomas and (2) there is no longer grade 4 designation; the new designation includes grade 1 (low grade, well differentiated), grade 2 (high grade, moderately differentiated), and grade 3 (high grade, poorly differentiated).

Tumor site, size, local spread and metastasis

In the 8th edition of the *AJCC Cancer Staging Manual* of bone, the pelvis and spine each have a separate and distinct TNM classification (not a separate stage grouping). This is due to the fact that smaller and anatomically confined sarcomas are prognostically favorable than larger and more extensively involved sarcomas. For staging purposes and based on the tumor site, bone sarcomas are grouped into three groups: (1) appendicular skeleton (extremities), trunk, skull, and facial bones; (2) pelvis; and (3) spine. For extremity and pelvic tumors less than or equal to 8 cm, tumor is designated as T1, and tumor greater than 8 cm is T2. For extremity sarcomas, skip lesions (discontinuous tumors in the primary bone site) are designated as T3 regardless of tumor size. For pelvic and spine sarcomas, the number of bone segments involved and extraosseous extension and beyond dictates a progressively higher stage. Tumor metastases include regional lymph nodes metastasis and distant metastasis involving lung, other bone, or other distant sites. Localized sarcomas are of lower stage with a better prognosis than sarcomas with metastases (higher stage).

High-grade sarcomas that are sensitive to chemotherapy are typically subject to neoadjuvant therapy, such as biopsy-proven high-grade osteosarcoma, Ewing sarcoma, or pleomorphic sarcoma. As stated in the 8th edition of the *AJCC Cancer Staging Manual* of bone, for patients with osteosarcoma or Ewing sarcoma, equal to or greater than 90% tumor necrosis after neoadjuvant chemotherapy indicates a better prognosis than those with less necrosis.

III. Typical gross photos of bone resection

Some examples of common bone tumors are illustrated in Figures 50-1 through 50-3, including giant cell tumor of bone (Figure 50-1), dedifferentiated chondrosarcoma (Figure 50-2), and mesenchymal chondrosarcoma (Figure 50-3).

Figure 50-1. Giant cell tumor of bone. This is a gross photo (longitudinal section) of a right distal femur involved by giant cell tumor (6 x 4.5 x 3.5 cm) with no prior treatment.

Figure 50-2. Dedifferentiated chondrosarcoma. This is a gross photo (longitudinal section) of a right proximal tibia involved by dedifferentiated chondrosarcoma (11 x 5 x 5 cm). Central aspect of tumor reveals tan, white-grey, cartilaginous tissue with surrounding tan-red/brown fleshy tissue. Tumor extends into soft tissue.

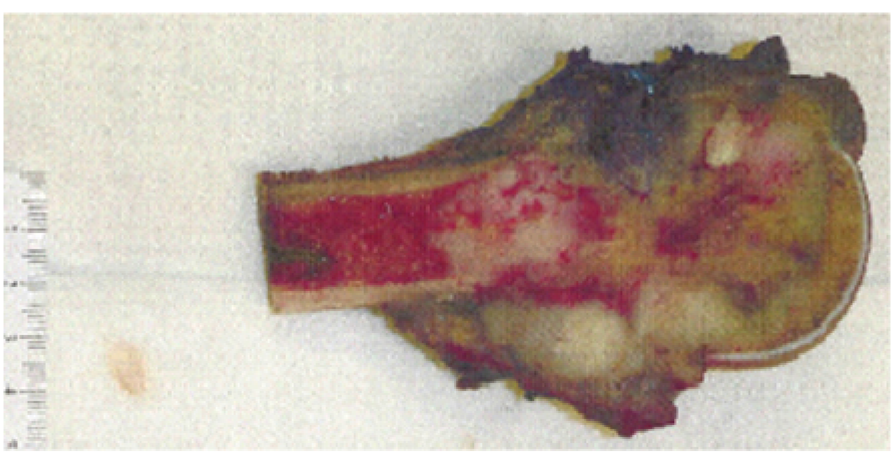

Figure 50-3. Mesenchymal chondrosarcoma. This is a gross photo of a right proximal humerus involved by mesenchymal chondrosarcoma (8.5 x 7 x 6.5 cm) with soft tissue extension including a mapped section. The tumor is tan-white to red-pink and fleshy with areas of firm grey-white cartilage.

IV. Dissection techniques: step-by-step description

1. Anatomic structures (eg, muscle, bone, nerve) and anatomic landmarks (eg, femoral head, tibia) and/or surgically designated sutures/ink must be identified (see Figure 50-4). If orientation is unclear, the surgeon should be contacted to provide additional information.

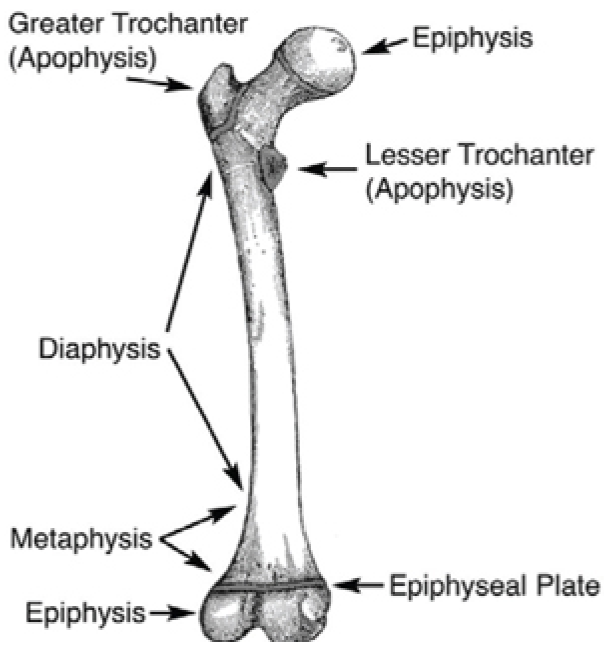

Figure 50-4. Common anatomic landmarks of long bones. Adapted from *Gray's Anatomy*.[4]

2. Ink margins or external surface (if unoriented) of specimens.

a. Before inking, blot specimen dry with a paper towel or gauze.

b. Pat ink on surface with a sponge, gauze, or cotton applicator. Do not pour ink over the specimen.

c. Unoriented specimens should be inked one color (eg, black or blue).

d. Oriented specimens with margins should be inked as follows:

Anterior/superficial – Yellow/Gold
Posterior/deep – Black
Superior – Blue
Inferior – Green
Medial – Red
Lateral – Violet

e. Change gloves if necessary to avoid introducing ink into the interior of the specimen.

f. After the ink has been applied, Bouin's solution or methanol should be applied. This acts as a mordant and helps to fix the ink to the tissue and prevent it from dissolving in formalin.

g. After inking the specimen, thoroughly dry before sectioning. This may be done using a manual fan, gauze, or by fixing the ink by dipping specimen in alcohol for about 30 seconds.

h. If ink is present on nonmarginal tissue, microscopic sections of such areas should be described adequately to avoid interpretation of ink as margin involvement.

i. Stapled margins: Carefully cut away staple line as close to the staples as possible because staples cannot be removed without shredding the tissue. The next closest tissue taken (inked) will be the margin. (Indicate in gross description that a new margin underlying the staple line is taken and submitted in cassette #X.)

3. Record specimen dimensions (centimeters), and, if required, weight (grams) should be taken on intact specimens prior to dissection and fixation.

4. Initial gross exam is directed towards determining the site and size of tumor, location and identity of structures invaded by tumor, vascular invasion, necrosis, prior biopsy/excision site (if applicable), distance from

resection margins, and presence of lymph nodes (if needed). (Note: document the absence of a lesion if the surgical intent was to remove one.)

5. It is important to correlate the gross examination information documented during the intraoperative consultation.

6. Triage tissue for special studies:

- If needed, fresh tumor can be frozen for diagnostic purposes, tissue triage for genomic studies, or used for long-term storage following tissue procurement protocols. The gross description should include an overall description of the excised specimen and of the tumor with measurements of each.
- Tissue that has been submitted for frozen section can be used for molecular analysis (DNA, RNA, fluorescense in situ hybridization [FISH], polymerase chain reaction [PCR], or reverse transcriptase [RT]-PCR). Freeze a portion (usually half) of the specimen and leave the remaining tissue for permanent sections. Do not freeze the entire specimen unless otherwise specified by a pathologist or clinician.
- Cytogenetic studies may be requested, and tumor tissue submitted must be viable and sterile. Roswell Park Memorial Institute (RPMI) medium may be used for such studies. Microbiologic cultures and smears may be requested if clinician is suspicious for an infectious process to be causing a bone mass. Please keep tissue as sterile as possible. Use sterile forceps, scissors, scalpels, etc, and submit representative sections of tissue in a sterile container. Adequately label container with patient's name, MRN, physician's name, type of specimen, and collection date/time. Submit to microbiology lab with filled out requisition of what cultures/smears are to be performed.
- Gouty specimens are submitted in alcohol not formalin.
- For any bony tumor, one extra block for molecular testing will be prepared by sampling the tumor without bony component, and this block should not be subjected to decalcification.

7. Describe the tumor location (epiphysis, metaphysis, or diaphysis) and whether it is confined to one compartment or extends into several compartments. For example, the tumor appears to have originated in the proximal tibial metaphysis but has extended through the posterior cortex to involve soft tissue and has also extended into the joint space. After photographing the specimen, in most instances a longitudinal slab of 0.5-cm thickness can be cut from the center of the specimen. The remaining two hemispheres of the tumor can then be serial sectioned ("bread-loafed") at 0.5- to 1-cm intervals in the plane perpendicular to the cut surface of the slab. The main slab will be entirely submitted with approximately 1 cm per cassette. Additional 1 cm of tumor from each cross-section of the remaining hemispheres of the tumor as well as sections that demonstrate the relationship between the tumor and the surrounding structures should also be submitted (see Figures 50-3 through 50-5).

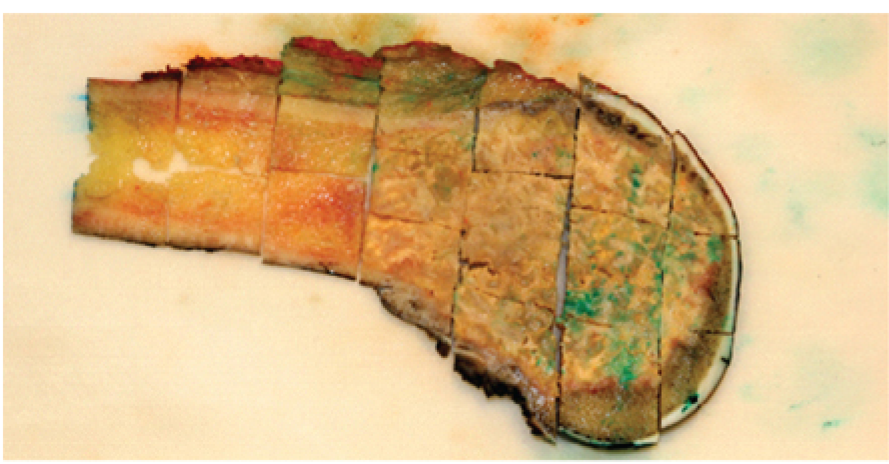

Figure 50-5. Giant cell tumor status post denosumab treatment. This is a gross photo (longitudinal section) of right distal femur involved by giant cell tumor treated with denosumab (7.4 x 5.6 x 5.3 cm). Tumor is irregular and tan-brown to yellow in color with areas of necrosis.

8. Sampling of the tumor to assess chemotherapy response is by taking one full cross-sectional slab of tumor at its greatest cross-sectional area. The center slab of tissue shall be photographed. The digital copy of the tumor slab is mapped and blocked out in its entirety (see Figures 50-5 and 50-6). Additional 1 cm of tumor from each cross-section of the remaining hemispheres of the tumor should also be processed. The percentage of viable tumor estimation by microscopic examination is calculated by the sum of all areas divided by the total cross-sectional tumor. The percentage of tumor necrosis is 1 minus the % of viable tumor cells.

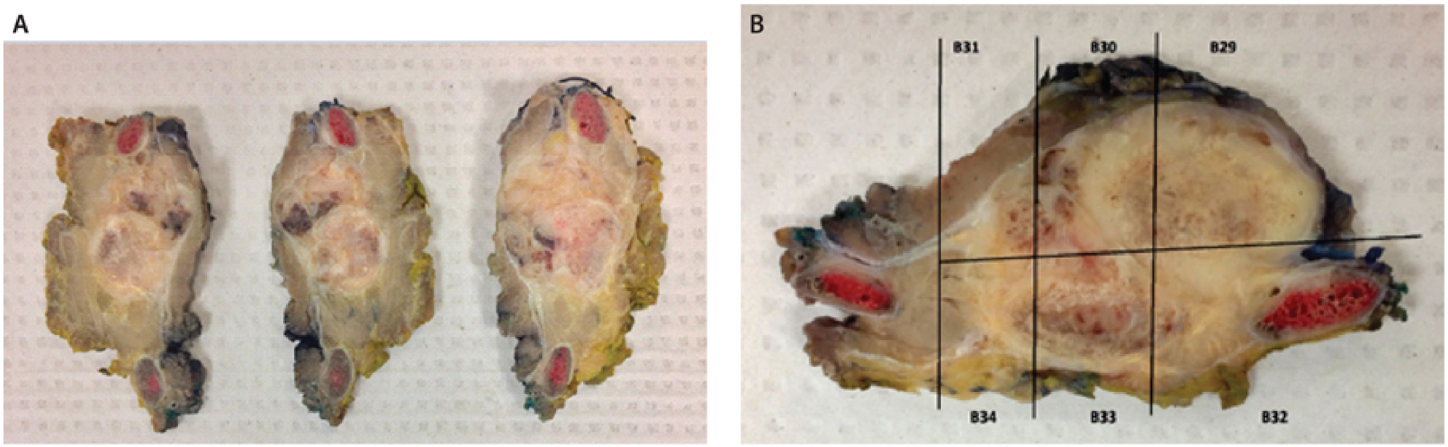

Figure 50-6. Ewing sarcoma. These gross photos demonstrate a Ewing sarcoma serially sectioned (A) and mapped (B) involving left ribs 9-11 (6.3 x 3.9 x 2.9 cm) status post neoadjuvant chemotherapy. Tumor is firm, ill-defined, and tan-white. There are focal areas of hemorrhage and necrosis.

V. Gross description using paragraph system

Bone tumor resection

1. Large resections for tumor including amputations usually involve either tumors of bone or cartilage, or soft tissue tumors with bone involvement.
2. Specify the type of specimen (above knee amputation, hip disarticulation, etc). Give the dimensions of each structure present, including length and maximum circumference of limbs.
3. Incise the soft tissue in a plane that will demonstrate the greatest extent of the tumor. Please take a photomicrograph of the cross-section of the specimen.
4. Describe the tumor including size, appearance (color, percentage of necrosis, bone formation, cartilage formation), location (tissue compartment), relationship to surrounding structures (bone, vessels, nerves, muscle), center of tumor (epiphysis, metaphysis, diaphysis, intramedullary, periosteal), erosion of cortex, extension into soft tissue (compression or true infiltration), extension through epiphyseal plate, extension into or across joint space, vascular involvement, skip metastases, and distance from each margin.
5. Take soft tissue sections of margins, representative structures (eg, vessels and nerves), and any areas of noncalcified tumor showing relationships to soft tissues. Carefully search for lymph nodes and submit.
6. Fix the entire specimen in formalin. After overnight fixation, decalcify the sections with bone. (Note: For all bone tumors, there must be a tumor block included that is not decalcified for possible molecular testing. Please choose from the soft tissue areas or minimal bony component.)
7. After decalcification, take sections of tumor to show relationship to adjacent normal bone, invasion of contiguous structures (eg, cortex, soft tissue, joint space), and margins. Indicate the location of sections taken on a diagram of the specimen. (Entire cross-section of tumor is mapped out and submitted for histologic examination.)

Sample dictation

Received fresh, labeled with the patient's name, and designated "specimen container" left distal femur is an above-the-knee amputation with disarticulation of the knee (8 cm). The distal femur is 10 cm in length and surrounded by skeletal muscle.

Centered within the metaphysis is a tan/brown tumor (5 cm) that occupies most of the medullary cavity. The tumor appears viable with focal areas of necrosis (estimated 10%). Focal hemorrhage is present. The tumor invades through the cortex medially, laterally and anteriorly extending into soft tissue medially forming a soft tissue mass (2 cm). The tumor does not grossly involve the joint space. The tumor is located 3cm cm from the proximal margin (blue ink), 2 cm from the posterior (black ink) and anterior margins (red ink), 1 cm from the medial (yellow) and lateral margins (orange ink) and 2 cm from the distal margin (green ink). There is an attached skin ellipse over the anterior/medial portion of the specimen, measuring 5 cm, with a centrally located well-healed surgical scar measuring 1.5 cm. There is a hemorrhagic/fibrotic biopsy cavity (1 cm) located 1 cm deep to the skin surface and adjacent to the tumor. The femoral artery and accompanying nerves and veins are present. A photomicrograph is prepared with the location of sections marked. Sections containing bone are fixed and decalcified prior to submission..

A1-A15: Complete cross-section of tumor including relationship to cortex, submitted from proximal to distal
A16: Tumor and medial margin, perpendicular
A17: Tumor and lateral margin, perpendicular
A18: Tumor and posterior margin, perpendicular
A19: Tumor and anterior margin, perpendicular
A20: Tumor and proximal margin, perpendicular
A21: Tumor and distal margin, perpendicular
A22: Proximal soft tissue margin, perpendicular
A23: Distal soft tissue margin, perpendicular
A24: Distal bone resection margin, perpendicular
A25: Proximal bone resection margin, perpendicular
A26-27: Additional tumor sections
A28: Skin with scar
A29: Biopsy site

VI. Common pathologic findings in bone resection

1. Osteosarcoma: Conventional osteosarcoma (osteoblastic, chondroblastic and fibroblastic variants) is most common (see Figure 50-7 and 50-8). Other histologic variants include telangiectatic, small cell, parosteal, periosteal, and high-grade surface osteosarcoma. The conventional osteosarcoma is usually a large mass that arises centrally in bone with infiltrative margin, destructive to cortex and involving the soft tissue. The matrix varies from tan-grey-white and gritty (osteoblastic or fibroblastic) or glistening (chondroblastic). Telangiectatic variant is very hemorrhagic.

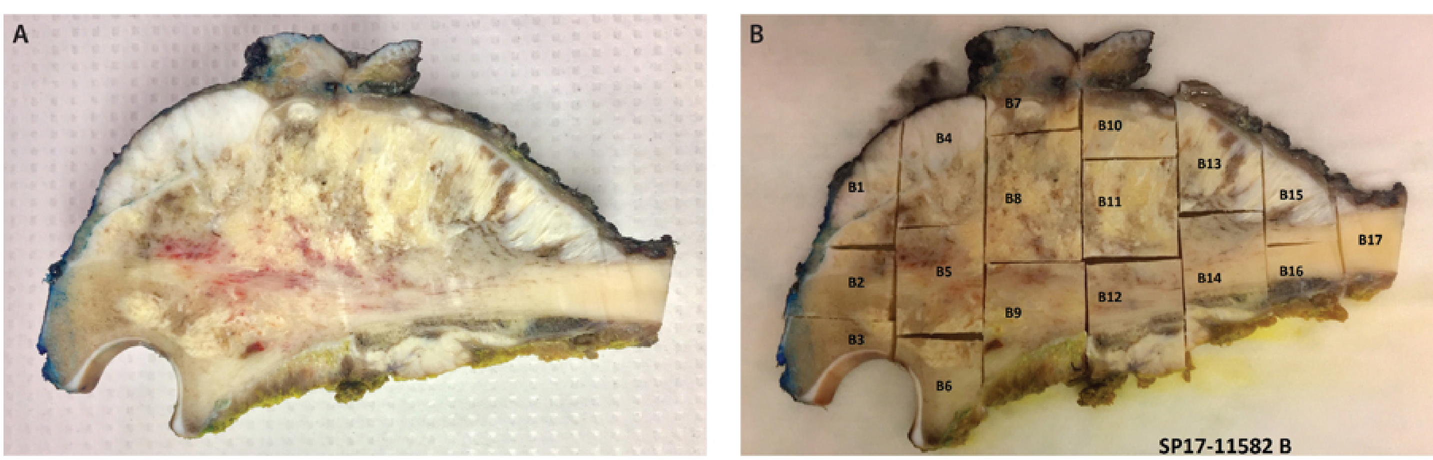

Figure 50-7. Chondroblastic osteosarcoma. A. This is a gross photo showing a right proximal ulna involved by chondroblastic osteosarcoma with extension into soft tissue, measuring 9.2 cm in greatest dimension. Tumor is ill defined, tan-white, with areas of necrosis and hemorrhage. B. This is a photo of mapped longitudinal section.

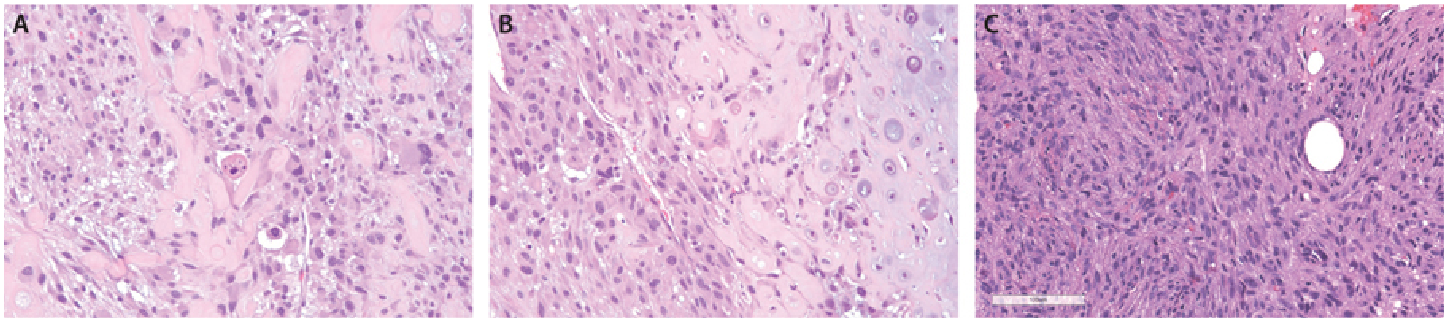

Figure 50-8. Osteosarcoma. A. Osteosarcoma, osteoblastic type, demonstrates predominantly neoplastic bone, which may be unmineralized (osteoid) or mineralized (H&E; 20X). B. Osteosarcoma, chondroblastic type, contains neoplastic cartilage, usually hyaline and high grade, but may be myxoid, and the neoplastic bone component can be very minimal (H&E; 20X). C. Osteosarcoma, fibroblastic type, contains malignant spindle cells of moderate to marked cytological atypia and can be associated with extracellular collagen, which can be extensive. The neoplastic bone component can be very minimal.

2. Chondrosarcoma: Conventional chondrosarcoma ranging from grade 1 to grade 3 histologic grades is most common (see Figure 50-9). Other histologic variants include dedifferentiated chondrosarcoma, mesenchymal chondrosarcoma, and clear cell chondrosarcoma (see Figures 50-2, 50-3, 50-10, and 50-11). The conventional chondrosarcoma typically arises centrally in bone. The gross specimen usually shows the cartilaginous cut surface. Higher grade chondrosarcoma involves the cortex that may break through the cortex with soft tissue invasion. Chondrosarcomas usually do not respond to chemotherapy or radiation therapy. Surgical resection is the main therapy. Accurate assessment of the tumor grade provides the single most prognostic information.

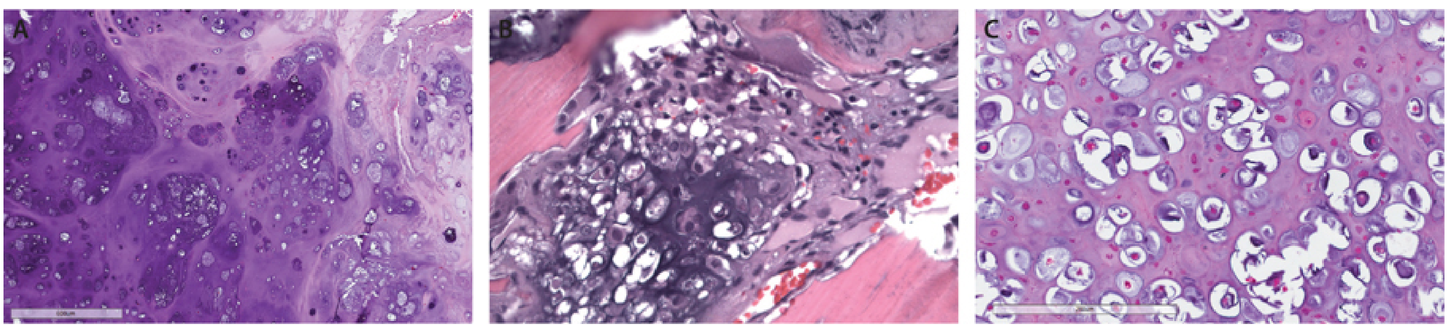

Figure 50-9. Chondrosarcoma. A. Chondrosarcoma, grade 1, is indistinguishable from enchondroma composed of low cellularity with no significant variation in size and shape of chondrocytes B. Chondrosarcoma, grade 2, has increased cellularity and atypia with hyperchromasia and increased nuclear size as well as binucleation (H&E; 20X). C. Chondrosarcoma, grade 3, is readily identified exhibiting high cellularity, pleomorphism, easily identified mitoses, and may even have necrosis.

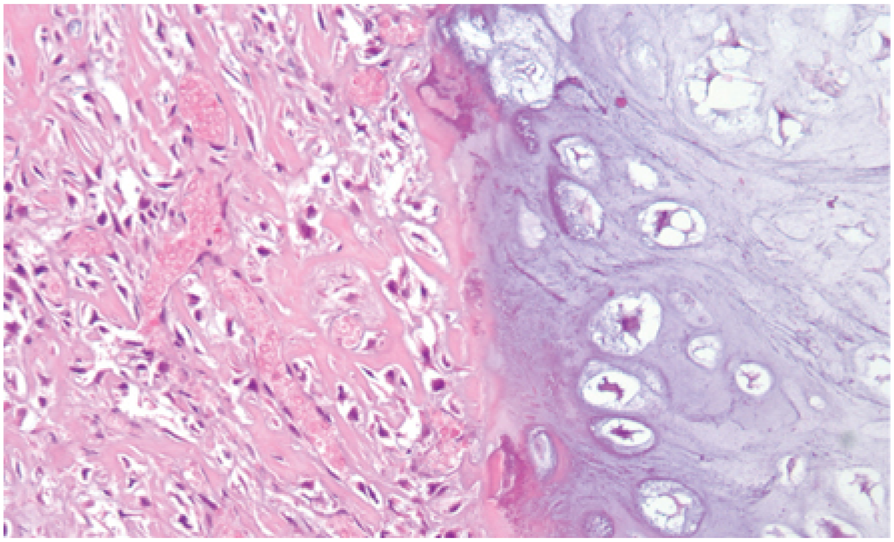

Figure 50-10. Dedifferentiated chondrosarcoma. There is an abrupt transition between the malignant cartilage and high-grade sarcoma (H&E; 20X).

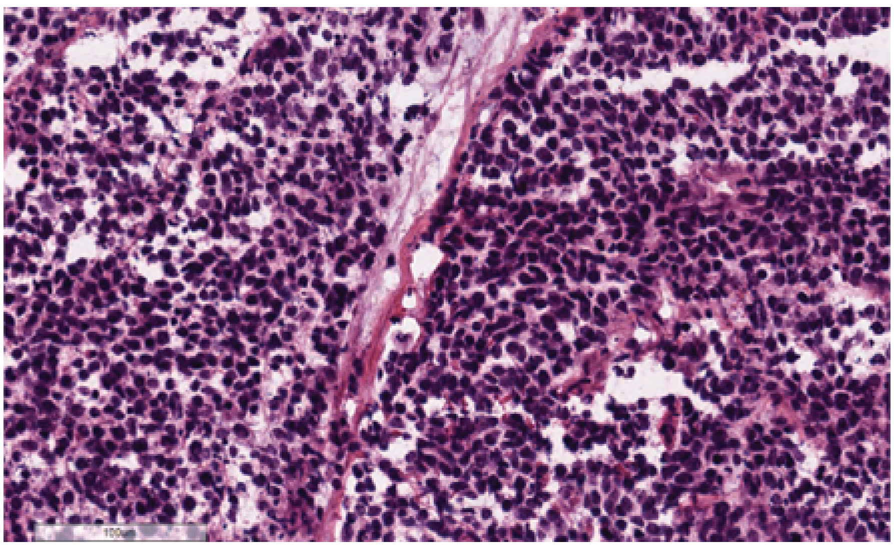

Figure 50-11. Mesenchymal chondrosarcoma. Area of tumor composed of Ewing sarcoma-like small round cells (H&E; 10X).

3. Ewing sarcoma: Ewing sarcoma is typically destructive of bone with infiltrative margin and larger associated soft tissue mass (see Figures 50-6 and 50-12). The cut surface is tan-grey. Hemorrhage and necrosis is a common finding. Triaging the specimen to facilitate molecular testing is expected in handling tumor tissue.

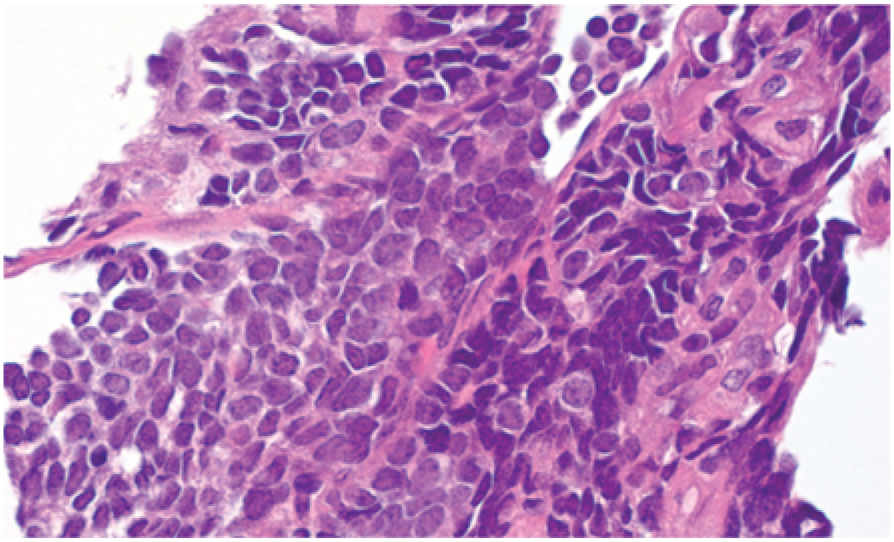

Figure 50-12. Ewing sarcoma. Small uniform round cells with round/ovoid nuclei containing fine chromatin and scant eosinophilic cytoplasm with indistinct borders (H&E; 60X).

4. Chordoma: Chordomas are typically confined within the bone (see Figure 50-13). The cut surface is mucoid or jelly-like. The dedifferentiated chordoma may have a more tan-grey and firm appearance. Dedifferentiated chordoma has a worse prognosis.

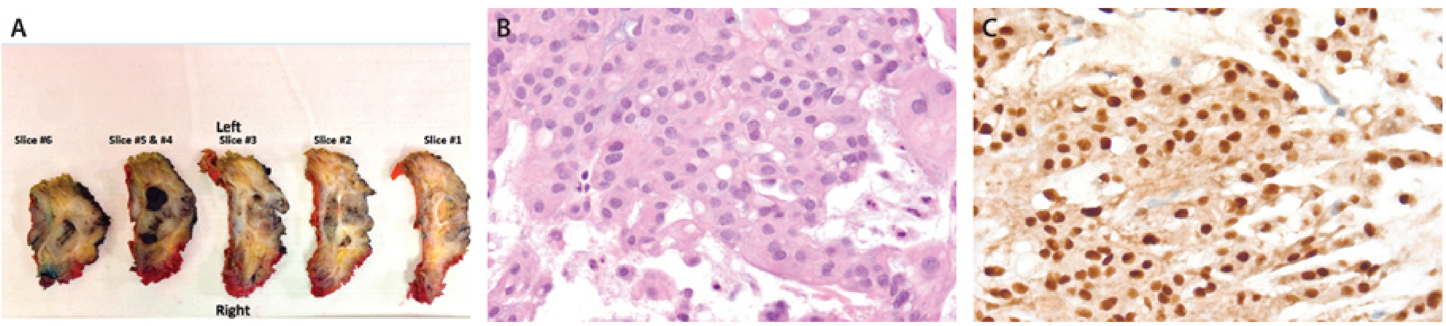

Figure 50-13. Chordoma. A. This is a gross photo of a coccyx, serially sectioned, involved by chordoma, grade 2 (2.3 x 1.8 x 1.3 cm). Tumor is lobulated with tan/grey color and focally hemorrhagic. B. Large epithelioid cells with eosinophilic to focally clear, vacuolated cytoplasm arranged in nests/cords within myxod matrix (H&E; 40X). C. The nuclei are immunoreactivity for brachyury (IHC; 40X).

5. Giant cell tumor: Giant cell tumor is a benign but locally aggressive tumor of bone (see Figure 50-1). The tumor is usually located in the epiphyseal/metaphyseal region with a large and well-defined mass that causes cortical thinning. The cut surface ranges from soft, red-brown to yellowish, firm depending on the presence of hemorrhage, histiocytic cells, and fibrous tissue. Giant cell tumor can undergo malignant transformation that becomes more destructive (see Figure 50-14). Giant cell tumor is typically treated with curettage. Complete en bloc excision results in less local recurrence.

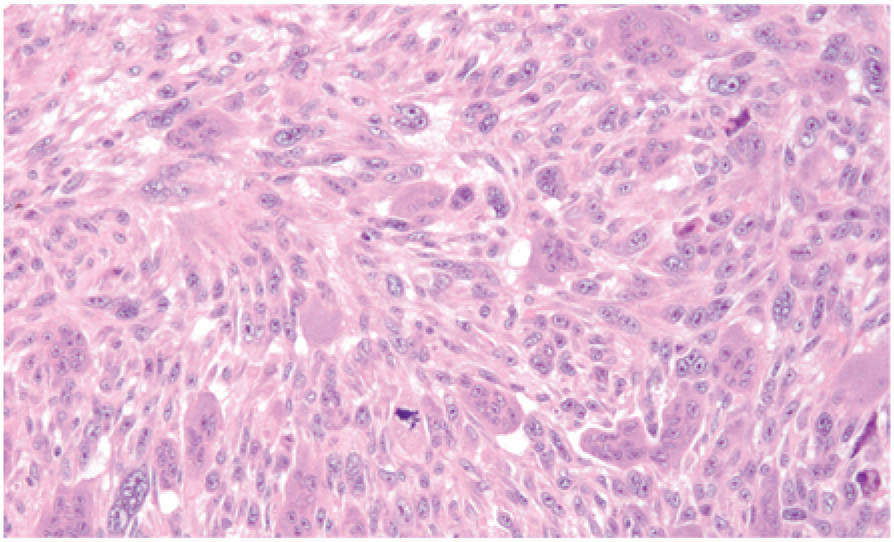

Figure 50-14. Malignant giant cell tumor. Tumor is composed of markedly atypical mononuclear cells with associated osteoclast-like giant cells and atypical mitotic figures (H&E; 10X).

VII. Common potential staging pitfalls and solutions

The most commonly used staging system in the United States is the American Joint Committee on Cancer (AJCC) staging system where primary bone sarcomas are staged based on the tumor's histologic type, grade, size, location, and tumor involvement (local spread, local and distant metastasis).

1. Primary malignant lymphoma and multiple myeloma are not staged using bone tumor protocol.
2. Bone sarcomas are staged based on tumor histologic type, tumor biological grade, three-dimensional tumor size, tumor location/multifocality/extent of involvement, and the presence as well as the location of metastasis. For example, if an osteosarcoma has skip lesions or satellite lesions, regardless of the size of the largest tumor, the primary tumor is T3. If a spinal tumor has gross vascular invasion or tumor thrombus in the great vessels, the tumor is T4b. If a large pelvic tumor spans three pelvic segments or tumor of any size crosses the sacroiliac joint, the tumor is T4. Regional lymph nodes are rare. Lung metastasis is most common. M1a is lung metastasis only, regardless of the numbers of lung metastases. Distant sites including lymph nodes define M1b status.
3. Because the anatomic site of the tumor influences the tumor outcome, pelvis and spine each have a separate and distinct TNM classification, whereas the appendicular skeleton, trunk, skull, and facial bones are grouped together.
4. The definition of AJCC TNM is summarized as pathologic stage classification (pTNM, AJCC 8th ed). The clinical stage is outside the scope of practice of a pathologist and will not be discussed in this chapter.

VIII. What to include in the pathology report?

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists and institutional requirements.

- Describe procedure performed and structures/organs present.
- Describe the tumor histologic type, biological grade, and three-dimensional size.
- Describe the location, extent of involvement, and focality of the tumor.
- Mitotic count, tumor necrosis, viable tumor cells.
- Angiolymphtic invasion.
- Margin status.
- Local and distant metastasis.

A demo report is provided below to demonstrate the necessary information to be included in a pathology report, and a synoptic template should be utilized.

FINAL DIANOSIS:

Right Proximal Humerus Mass, Radical Resection:
Dedifferentiated chondrosarcoma, WHO grade III, tumor measures 12 x 9.5 x 6.5 cm.
Tumor involves the proximal humerus medullary cavity, cortex and the right upper arm soft tissue.
Tumor necrosis is less than 50%. Mitotic count is up to 5/10 HPFs.
Angiolymphatic invasion is focally present.
Surgical margins are free of tumor.
Pathologic stage: pT2NX.

Synoptic report

The following information is a modification of the AJCC cancer staging protocol and College of American Pathologists (CAP) cancer staging protocol for bone tumor resection. This protocol is not required for primary resection specimen without any residual sarcoma following neoadjuvant therapy, plasma cell neoplasms, lymphoma, pediatric Ewing sarcoma, or soft tissue sarcoma involving bone.

VIX. Pediatric Ewing sarcoma

The CAP protocol for the examination of resection specimens from pediatric patients with Ewing sarcoma is pertaining to specimens designated resection, amputation, and limb salvage procedures. Ewing-like sarcoma, including *CIC*- or *BCOR*-rear-ranged sarcoma or biopsy procedures are not applicable to this. Formalin-fixed tissue for histologic evaluation is the first priority of grossing, while tissue procurement for ancillary testing for diagnostic, prognostic, and predictive purpose is the secondary priority.

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51. Heart and Great Arteries

Dylan V. Miller, MD

Introduction

This chapter covers the evaluation and reporting of primary tumors resected from the heart, aorta, and pulmonary artery. These tumors are exceedingly rare, and evidence on which to base a staging system to predict prognosis and survival time, as well as provide treatment recommendations, is lacking. What evidence is available consists of small series and single-center reports.[1-4] Because of this, these tumors are not included in the American Joint Committee on Cancer (AJCC) staging manual.

Still, if such evidence is ever to be accumulated in a robust and systematic fashion (by multicenter registries, for example), a standardized and uniform approach to describing the clinical, surgical, gross anatomic, and histologic features of these tumor specimens is needed. In recognition of this, the College of American Pathologists (CAP) created a cancer protocol template[5] in 2009 (which is now "retired"), and the International Collaboration on Cancer Reporting (ICCR) created a dataset in 2015.[6] These will serve as the sources for recommendations in this chapter.

Benign tumors of the heart are included in this chapter. Because these can arise in "sensitive" anatomic locations within the heart (such as the atrioventricular node) and potentially cause obstruction and other cardiac complications, even at a small tumor size, benign cardiac tumors have potential to cause death. They may also recur and be associated with poor prognosis after surgery. This is despite the fact that these tumors do not show histologic invasion or enter lymphatics. Tumors arising within the cardiac chambers also have immediate access to "hematogenous" spreading to the lungs (for right-sided tumors) and systemic circulation (for left-sided tumors). There is some precedent for including benign tumors in cancer staging schemes (such as typical carcinoid tumor in the lung and schwannoma in the central nervous system). Mesothelioma and primary cardiac hematolymphoid neoplasms are not covered in this chapter but are discussed elsewhere in the book.

While some tumors may be accessed and biopsied endovascularly, open surgical removal is the primary treatment modality for most cardiac tumors if they are deemed to be resectable by imaging studies. The nature of tissue sampling (eg, catheter bioptome or computed tomography [CT]-guided needle core) or extent of resection (incisional biopsy, wide resection, or explantation at time of transplant) are important to include in the report. For most resections, a portion of normal cardiac tissue will be included for the assessment of margins as well.

I. Indications for cardiac tumor resection

1. Incisional biopsy and subtotal resection
   A. In some cases, complete gross removal of tumor is not possible, such as when critical cardiac structures are involved. "Debulking" the tumor may still be of value in relieving obstruction or reducing embolic potential, so incomplete excision is performed.
2. Wide resection
   A. Complete resection of atrial masses typically includes removing a portion of the atrial wall (most often the atrial septal wall) attached to the tumor with subsequent patch repair of the resulting defect.
   B. Excision of valve-based masses may involve complex repair or complete replacement of the valve to maintain competency of the valve after the leaflet from which the tumor arose is removed.
   C. Removal of intramural ventricular masses is typically done while trying to preserve as much intact myocardium as possible. A thin rim of ventricular myocardium may be present around the tumor in these specimens.
3. Explantation

A. Inoperable tumor is a rare and controversial indication for cardiac transplantation, but such cases have been reported, especially for biologically benign tumors.

II. What do we expect to see in the cardiac tumor resection specimen macroscopically and microscopically?

1. Intracavitary masses

Tumors arising from the wall of a cardiac chamber and growing into the luminal space are the most common type in terms of growth pattern. Statistically, the left atrium is by far the most common site for these. A portion of the normal chamber wall attached to the tumor is included with these specimens and should be treated as a surgical margin. Almost any of the primary cardiac tumor types can assume this configuration, but the most common histologic types include myxoma, papillary fibroelastoma, and various sarcomas.

2. Valvular masses

Tumors arising from the valve leaflets usually necessitate excision of the entire leaflet or the entire valve. The margin of the valve (where the surgical incision separated it from the valve annulus) should be treated as a surgical margin. Any of the valves may be involved, although the mitral valve seems to be the most common. Papillary fibroelastomas, myxomas, and sarcomas are also the most frequent histologic types in this location.

3. Intramural masses

Removal of tumors growing within the walls of the ventricles is substantially more complicated and care is taken in developing a dissection plane between the tumor and myocardium without entering the tumor (and potentially causing tumor spillage). Usually the entire outer surface is considered a surgical margin and shows adherent strands of myocardium. The most common intramural masses include rhabdomyoma, fibroma, hamartoma of mature cardiac myocytes, lipoma, vascular tumors, and sarcomas.

4. The great arteries

Primary tumors of the aorta and pulmonary artery (intimal sarcoma and angiosarcoma) are usually highly invasive and include both a prominent intraluminal component and some extension through the arterial wall into surrounding mediastinal tissue. Resection usually involves removal of a portion of the artery itself. The proximal and distal arterial wall margins as well as the "radial" margins around the tumor should be considered surgical margins.

III. Typical gross photos of heart resection specimens

Gross photographs are often of interests to cardiac surgeons who procure these specimens and have great utility in reports and teaching conferences as well as correlation with the findings of various imaging modalities (echocardiogram, magnetic resonance imaging [MRI], etc) performed on these patients preoperatively.

- For the most common benign cardiac tumors, such as atrial myxoma, various features of interest should be documented in photographs (Figures 51-1 through 51-3). These include the stalk and patch of atrial septum that is often removed as part of the resection, as well as the outer capsule and cut surface.
- For sarcomas and other malignancies, the tumors may be removed piecemeal or in such a fashion that orientation with respect to recognizable structures may be difficult. If an identifiable anatomic structure is present, the relation of this to the mass should be depicted in the gross photograph (Figure 51-4).
- Papillary fibroelastoma presents a unique challenge for gross photography, since the impressive frond-like architecture is best appreciated when the tumor is suspended in a clear liquid (formalin, ethanol, or water) (Figure 51-5).

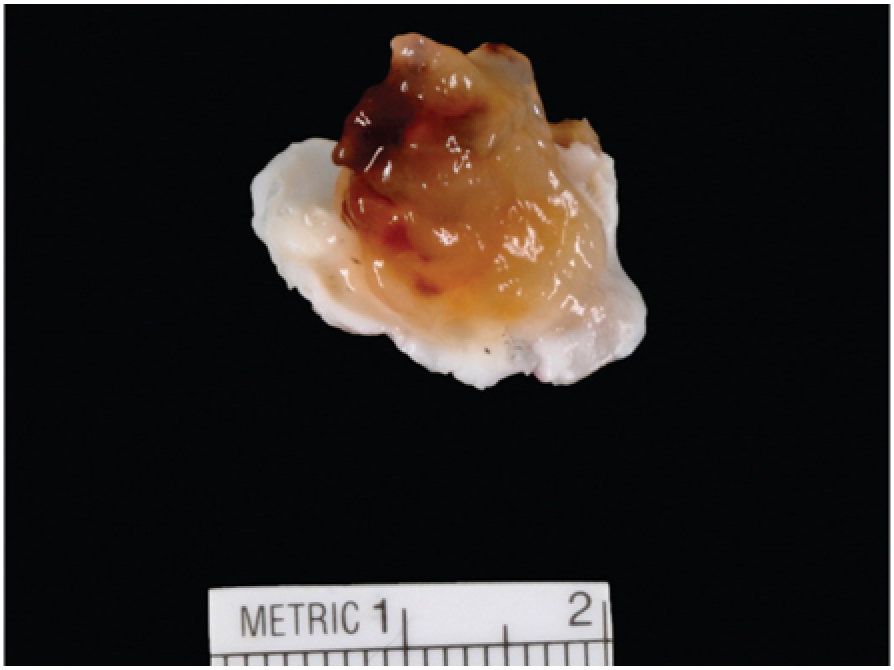

Figure 51-1. Small atrial myxoma specimen. Note the gelatinous/mucoid appearance of myxoma. The base in the example is broadly attached to the white patch of atrium excised along with the tumor.

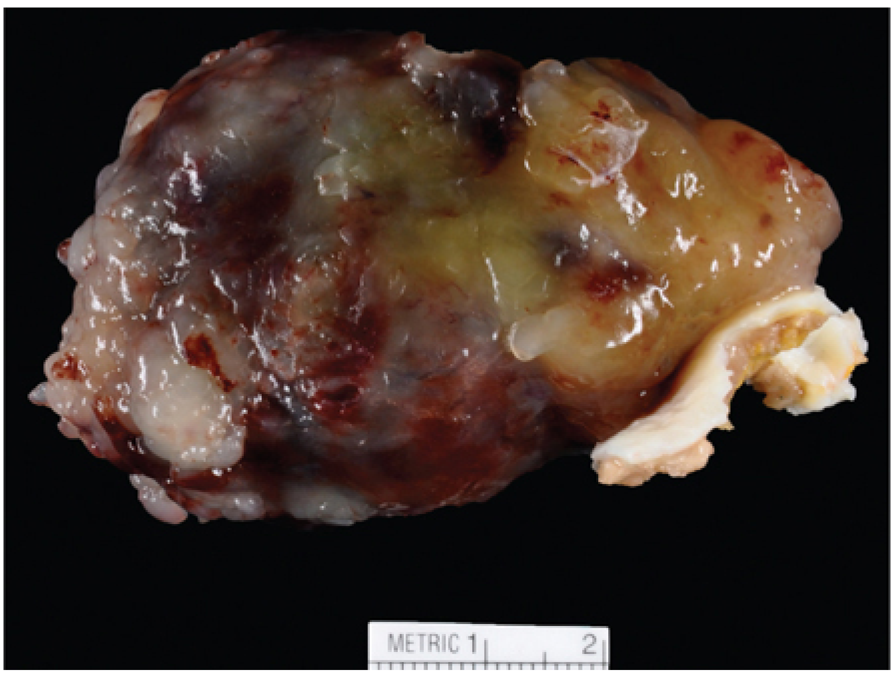

Figure 51-2. Large atrial myxoma. This larger example of myxoma is more pedunculated, but again with an obvious portion of atrial wall attached to the right.

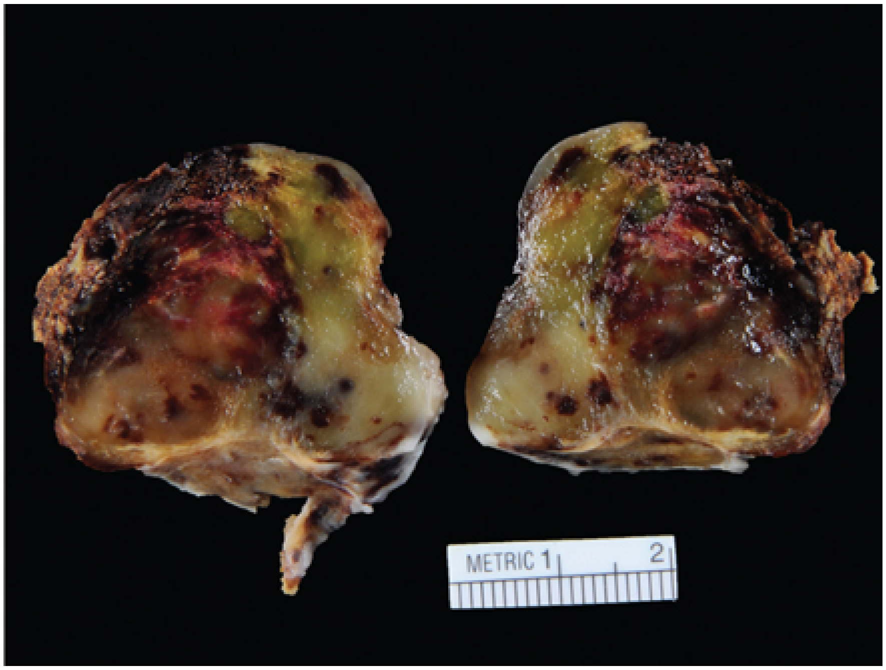

Figure 51-3. Atrial myxoma (cut surface).

Figure 51-4. Sarcoma attached to mitral leaflet (arrows).

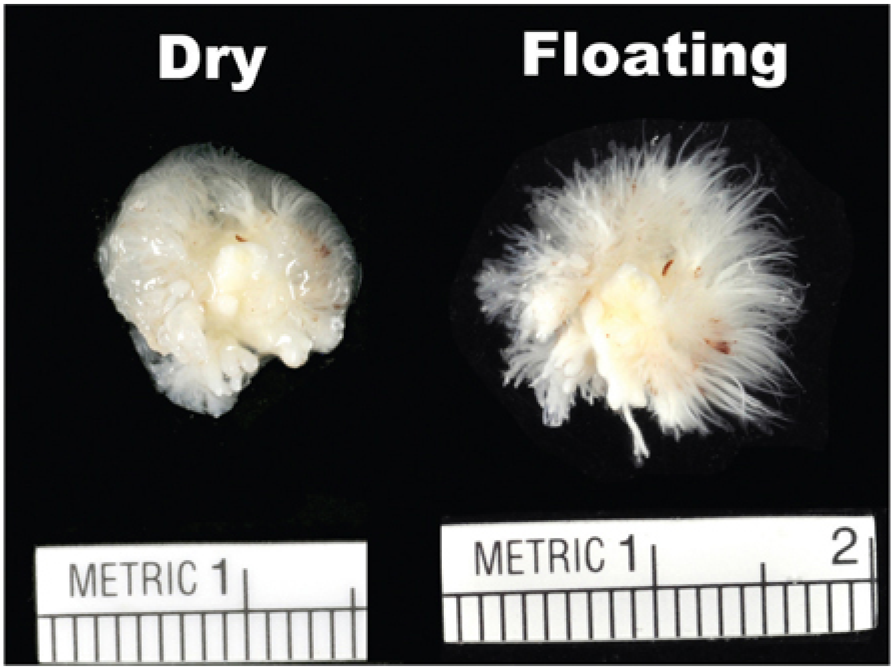

Figure 51-5. Papillary fibroelastoma. This sea anemone-like tumor is a papillary fibroelastoma that was present on an aortic valve leaflet. When these specimens are dry they can mimic the gelatinous appearance of myxoma, but suspending in clear liquid (like formalin) makes the frond-like appearance more apparent.

IV. Dissection techniques: step-by-step description

1. Review relevant clinical history and imaging studies (echocardiogram, cardiac CT and cardiac MRI).

It is important to review all available imaging studies since these serve as a surrogate for the gross pathology of surgically resected specimens. With the exception of explant specimens, it is difficult to properly orient and identify portions of normal structures that may be attached without this helpful information.

2. Orient the specimen.

Where possible, it is important to orient any cardiac tumor specimen and determine if surgical margins of interest are present, so they can be inked and sectioned appropriately. As mentioned before, these could be patches of atrial or ventricular wall, cut edges of valve leaflets, arterial walls, or circumferential excision margins. The surgeon may assist in orientation by placing a suture or other markings and may be directly consulted in cases where confusion remains. It should be noted that margin positivity may not lead to the taking of additional margin tissue or, in fact, any alteration of the treatment plan postoperative. Still, for the sake of accurate registry data and garnering prognostic evidence, recording the margin status accurately is still important.

3. Record the specimen dimensions and/or weight and separately describe the tumor mass and any normal structures (as applicable).

Describe any tumors identified. These data are important, but the approach does not differ substantially from the handling of any other tumor specimen type.

4. Dissect the specimen in a way that best demonstrates the pathology, and sample the tumor for light microscopy.

Taking sections that demonstrate involvement of normal structures or that allow for measuring the distance to the nearest margin is helpful. Gross photographs before and after specimen dissection are also invaluable, especially given the scarcity of these tumors. If the tumor is grossly heterogeneous, submitting blocks that represent each gross appearance is suggested.

V. Gross description of cardiac tumor specimens

As in previous chapters, Raymond's paragraph system will be used to describe the cardiac tumor specimens.

Example of gross description of cardiac tumor specimens

Intracavitary masses

Specimen consists of a pedunculated gelatinous tan-red mass (23 g, 4.8 x 3.2 x 2.0 cm) with an apparent stalk attachment to a portion of atrial wall. The atrial wall patch measures 1.2 x 0.9 cm and shows red-brown myocardium at the deep aspect. The deep and peripheral margins of the atrial patch are inked black and the entire specimen is bisected longitudinally in a plane that divides the stalk and atrial patch attachment. Sections showing the mass, stalk, and atrial patch in continuity are submitted from each half in A1 and A2. The remaining atrial patch tissue is submitted in A3 and representative sections of the main mass are submitted in blocks A4-A10.

Intramural masses

Specimen consists of a firm, spherical to slightly ovoid mass with adherent bands and strips of myocardium circumferentially around the entirety. The mass weighs 28 g and measures 4.1 x 3.8 x 3.0 cm. Ink is applied to the entire specimen. The specimen is serially sectioned in 5-10 mm slices revealing a white fibrous cut surface that lacks a well-defined capsule. The closest margin appears to be <1 mm from the inked surface. Representative sections are submitted in A1-5, with the closest margin in A2.

Valvular masses

Specimen consists of a firm tan-pink mass (5.2 x 3.4 x 3.0 cm) with an apparent portion of mitral valve leaflet intimately attached at the tumor base. The leaflet measures 1.2 x 0.5 x 0.2 cm, and the leaflet free edge is inked black. The specimen is bisected longitudinally in a plane through the middle of the mitral leaflet. Sections showing the mass infiltrating the leaflet, including the inked leaflet free edge are submitted in A1-A3. Additional representative samples of the mass are submitted in A4-A5.

Great artery tumors

Specimen consists of a soft friable red-purple mass measuring 2.7 x 2.2 x 2.0 cm with a portion of unoriented aortic wall attached at the base. The aortic wall tissue measures 3.5 x 2.5 x 0.2 cm. The adventitial aspect and peripheral margins of the aortic wall are inked black, and the specimen is serially sectioned. The central cross-sections appear to show invasion into the wall, but not into surrounding peri-adventitial soft tissue. The specimen is entirely submitted in blocks A1-A8.

Explant

A cardiac explant specimen is received, weighing 415 g. There are shaggy fibrinous adhesions at the left anterior and lateral apex. The anterior surface of the heart is inked black. Short axis cross-sections through the ventricles are laid out sequentially and show a tan-white mass in the anterior septal myocardium that extends anteriorly to the right and left ventricular myocardium. The mass extends from the mid ventricle (papillary muscle level) to the apex and focally extends through the epicardium in the area of pericardial adhesions. The mass measures 5.6 x 3.8 x 2.1 cm. The mass is several centimeters from the caval, atrial, and arterial resection margins. The uninvolved ventricle wall thicknesses are: left – 1.5 cm, septum – 1.4 cm, right – 0.4 cm. The remaining basal portion of the heart is then examined in the order of blood flowing thought the heart. The right atrial appendage is present and without thrombus. The oval fossa is fused. The mitral valve appears normal, as does the right ventricle outflow and pulmonary valve (three leaflets, thin and pliable). The left atrial appendage is also present and without thrombus. The mitral leaflets are thin and pliable, without vegetations. The left outflow tract and aortic valve are likewise normal appearing. The valve circumferences are: tricuspid – 13.1 cm, pulmonary – 7.2 cm, mitral – 10.1 cm, and aortic – 7.3 cm. The coronary arteries are serially crossed-section in-situ and show at most grade 1 (25%) stenosis of the mid left anterior descending coronary artery (LAD) with no other lesions present. There is right coronary dominance. Sections are submitted as follows:

A1-A5: Anterior septum tumor (closest tumor approach to epicardium in A3)

A4: Posterior wall of left ventricle, mid ventricular level (uninvolved)

A5: Lateral wall of right ventricle

A6: Mid LAD cross-section

VI. Common pathologic findings in cardiac resection specimens

The inclusive list of recognized cardiac neoplasms is encompassed by the most recent World Health Organization "blue book."[7] The more common entities include:

Heart

Benign

- Rhabdomyoma
- Myxoma
- Papillary fibroelastoma
- Haemangioma
- Fibroma
- Cystic tumour of the atrioventricular node
- Other (specify)

Malignant

- Angiosarcoma
- Undifferentiated pleomorphic sarcoma
- Myxofibrosarcoma
- Other (specify)

Tumours of uncertain behaviour

- Inflammatory myofibroblastic tumour
- Paraganglioma

Pericardium

- Solitary fibrous tumour
- Germ cell tumour
- Angiosarcoma

Great vessels

- Angiosarcoma
- Intimal sarcoma subtype
- Leiomyosarcoma
- Other (specify)

VII. Common potential staging pitfalls and solutions

Not applicable (no AJCC staging system).

VIII. What to Include in the pathology report

The final pathology report should include as much detail and information as possible, recognizing that reporting styles may vary among pathologists.

- Describe the procedure performed and the nature of the specimen (eg, left atrial mass with atrial septal stalk).
- Provide the histologic type and grade (where applicable).
  - For sarcomas, use the French Federation of Cancer Centers Sarcoma Group system or National Cancer Institute's system, but clarfify which system is used.
- Is there visceral pleura invasion?
- Is the tumor limited to the lung or does it involve other structures included with the specimen?
- Where is the tumor located? Try to identify the segment, if possible. Does the tumor extend into an adjacent lobe?
- What is the status of the margins?
- Did the patient receive neoadjuvant chemotherapy and/or radiation? If so, is there any treatment effect?

A sample report is provided below to demonstrate the necessary information to be included in a pathology report. Use of a synoptic template is strongly encouraged.

FINAL DIAGNOSIS:

Heart, Right Atrial Mass, Resection:

- Angiosarcoma, high grade (NCI Grade 3).

- The tumor measures 3.8 cm in greatest dimension and involves the right atrial wall.
- Resection margins are negative for malignancy (2 mm from medial margin).
- Please see the synoptic report below.

Synoptic report

The following information is a modification of the ICCR Dataset for Neoplasms of the Heart, Pericardium, and Great Vessels.

Neoadjuvant Therapy: Not administered

Operative Procedure: Resection

Specimen Integrity: Intact

Tumour Site(s): Right atrium

Tumour Focality: Unifocal

Maximum Dimension of Primary Tumour: 38 mm

Block Identification Key: A1–A5: Right atrial mass

Histologic Tumor Type: Angiosarcoma

Histologic Grade: Grade 3

Necrosis: Present

Extent of necrosis: 30%

Mitotic Count: 23 per mm^2

Extent of Invasion: Right atrial wall

Response to Neoadjuvant Therapy: Cannot be assessed

Margin Status: Not involved

Lymphovascular Invasion: Indeterminate

Method of evaluation: Routine staining (H&E)

Ancillary Studies: Not performed

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52. Lung

Paul Wawryko, MD; Brandon T. Larsen, MD, PhD; Mathieu C. Castonguay, MD

Introduction

This chapter covers the spectrum of pulmonary resection, focusing on those obtained in the context of neoplasia. Surgery is the primary treatment modality for most early stage (stage I and II) lung cancers and an important component of the multimodality treatment of locally advanced (stage IIIA) lung cancers. Surgery is typically planned based on clinical and radiologic findings, often without the need for preoperative biopsy of the primary tumor. Preoperative mediastinal lymph node evaluation, performed using a variety of techniques, including mediastinoscopy/mediastinotomy or transbronchial sampling with endobronchial ultrasound (EBUS) guidance, also assists in treatment planning. Surgery carries the risks of intraoperative mortality and postoperative complications in addition to reducing pulmonary function in patients who often have limitations secondary to the detrimental effects of smoking. The information obtained through pathologic examination of these specimens will help determine the need for additional treatment and provide prognostic information. Therefore, it is important for the gross examination and sampling of a specimen to be organized and thorough to facilitate the creation of an informative, succinct pathology report.

I. Indications for pulmonary resection

1. Lobectomy

A. Lobectomy is the current standard of care for lung cancer resection, primarily used in early-stage and locally advanced non-small cell lung carcinomas but also occasionally in carcinoid tumors and localized small cell carcinomas. Examples of lobectomy specimens can be seen in Figures 52-1 and 52-2.

Figure 52-1. Medial surface of a left upper lobectomy specimen (post inflation/fixation).

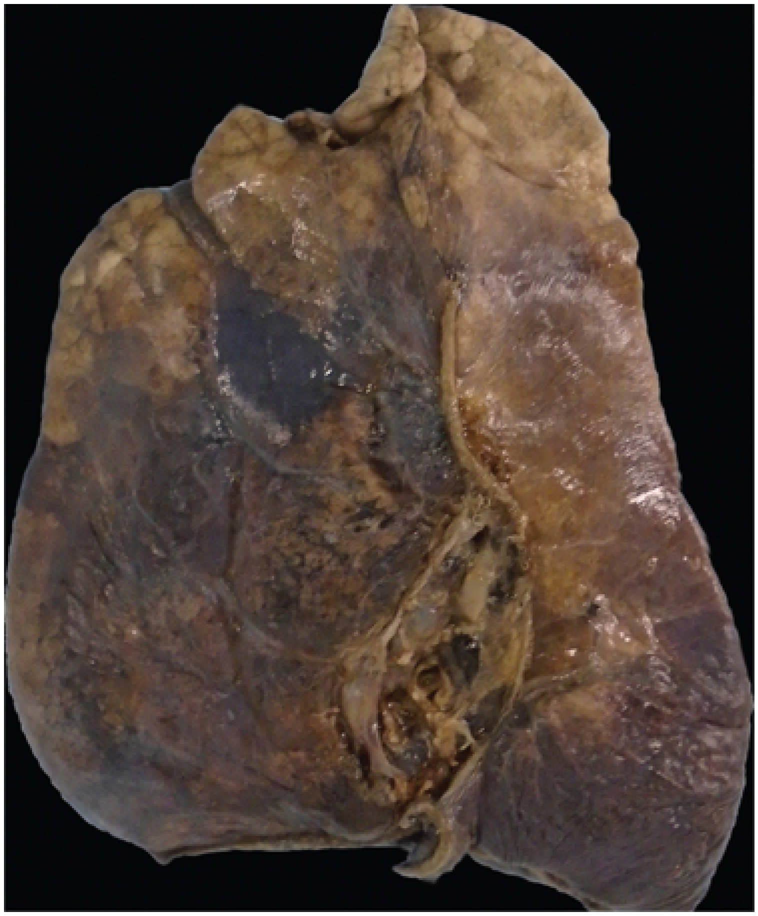

Figure 52-2. Medial surface of a right lower lobectomy specimen (post inflation/fixation).

2. Sublobar resection (eg, wedge resection or segmentectomy)

A. Sublobar resection may be offered to patients with stage I non-small cell lung carcinoma, often as a compromise to preserve as much lung tissue as possible in patients who have significant comorbidities or limited pulmonary function that makes them unsuitable for lobectomy. Sublobar resection carries an increased risk of local recurrence compared with lobectomy.

B. Wedge resection may be performed in a variety of clinical scenarios including evaluation of a lung abnormality with equivocal features of malignancy by imaging (eg, a ground-glass opacity or an area of persistent consolidation) or in the context of multiple lung nodules to determine primary or metastatic origin. An example of a wedge resection specimen can be seen in Figure 52-3.

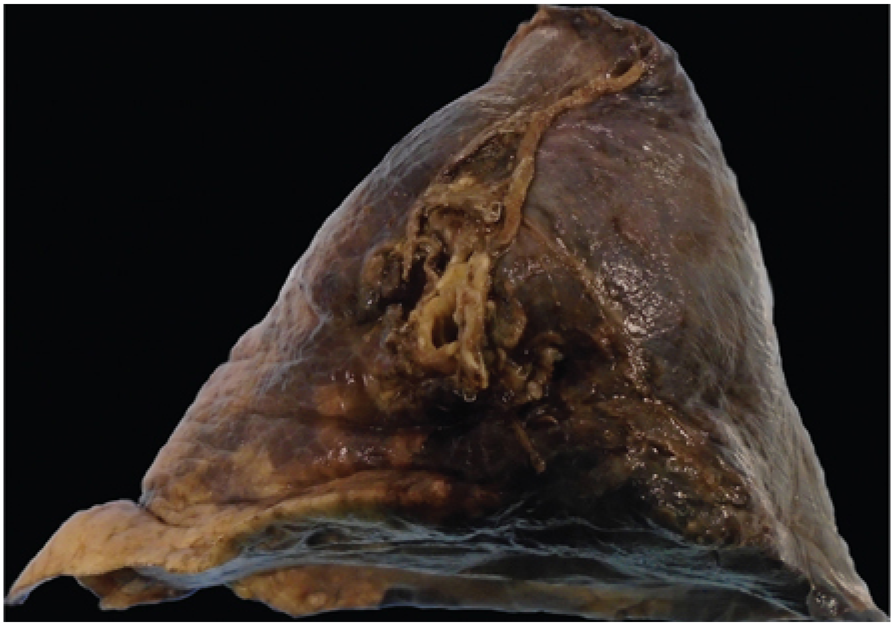

Figure 52-3. Pulmonary wedge biopsy specimen.

3. Pneumonectomy
A. In cases where lobectomy cannot completely remove the entire tumor, a pneumonectomy (or sometimes a bilobectomy) may be performed. This situation may arise when the primary tumor is in proximity to the primary bronchus or when there are multiple nodules within separate lobes but not involving the contralateral lung.
B. An extrapleural pneumonectomy, with the additional removal of the ipsilateral parietal pleura, hemidiaphragm, and portion of pericardium, may be performed in patients with malignant mesothelioma confined to the chest cavity (this topic is presented in its own separate chapter and will only be briefly mentioned here).
4. En bloc resection of additional tissue
A. In some cases of locally advanced non-small cell lung carcinoma where the primary tumor is determined to be surgically resectable, the specimen may incorporate additional structures, such as portions of chest wall, diaphragm, pericardium, or mediastinum.

II. What do we expect to see in the lung resection specimen macroscopically and microscopically?

Based on the above indications, the expected finding is a non-small cell carcinoma, typically adenocarcinoma or squamous cell carcinoma, presenting as a single solid lung tumor. Though not definitive, there are some clues to the histologic tumor type based on gross findings: adenocarcinomas most commonly arise in the periphery of the lung, whereas squamous cell carcinomas often arise centrally (see Figure 52-4); in addition, squamous cell carcinomas often cavitate, a finding often noted on imaging studies.

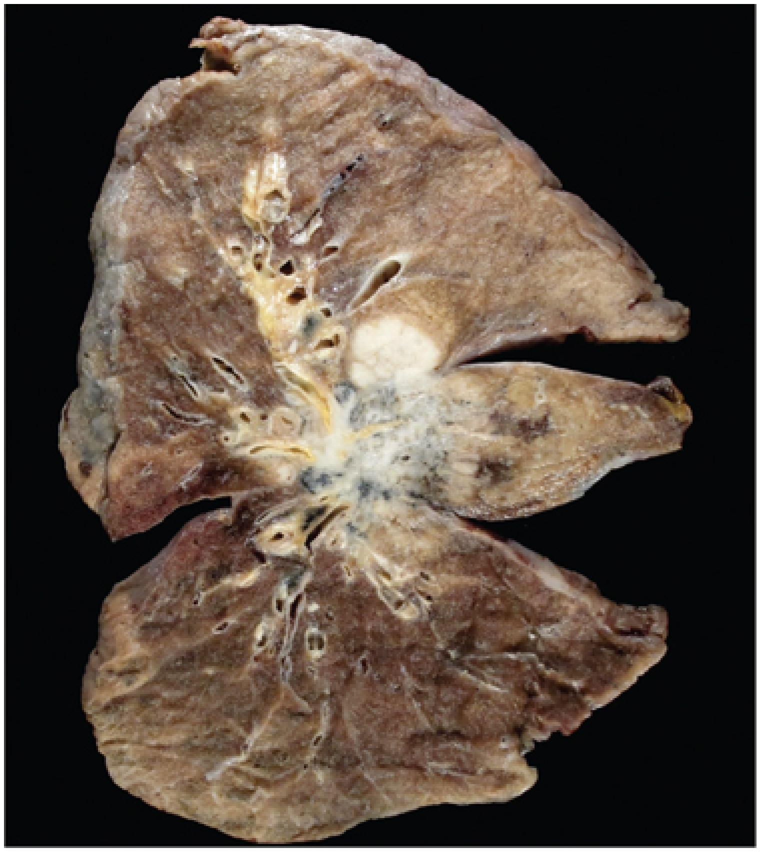

Figure 52-4. Squamous cell carcinoma in a right pneumonectomy specimen.

Staging lung cancers is not as straightforward as some other organs, which rely on just one parameter for pT category, but many of the staging parameters in lung can be assessed on gross examination alone, with confirmation of findings by microscopy.

The most basic element for staging lung cancer is the tumor size, with increased size associated with a higher pT category. Another important staging parameter, visceral pleural invasion, is often suggested by puckering of the pleura overlying the tumor. Tumor focality, a parameter that can significantly increase the pT category (or pM category), relies on the identification of additional nodules on gross examination (see Figure 52-5). Findings that are considered indicators of more advanced disease also include direct invasion of other structures, such as the main bronchus, chest wall, or mediastinum.

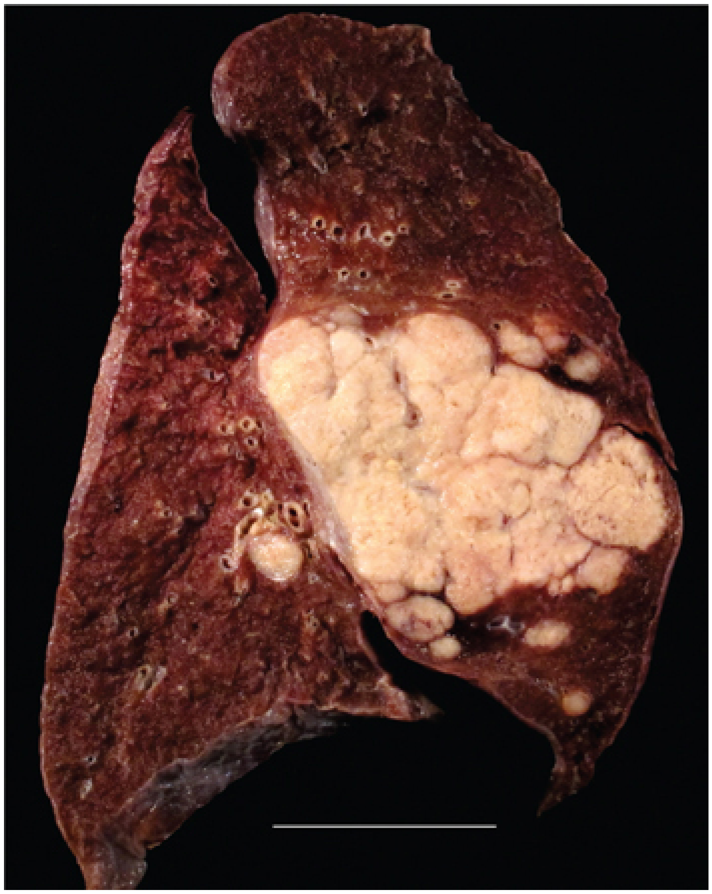

Figure 52-5. Adenocarcinoma in a left pneumonectomy specimen (pT4 based on metastasis to another ipsilateral lobe).

Sometimes cancers do not present as well-defined solid tumors. Adenocarcinomas with a significant lepidic component (ie, adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic-predominant invasive adenocarcinoma) may be more challenging to identify on gross examination and may only show a subtle thickening of the lung parenchyma (see Figure 52-6). Mucinous-type adenocarcinomas (eg, invasive mucinous adenocarcinoma, colloid carcinoma) may show an area of mucoid consolidation (see Figure 52-7). Some adenocarcinomas may present as diffuse pleural thickening, mimicking mesothelioma.

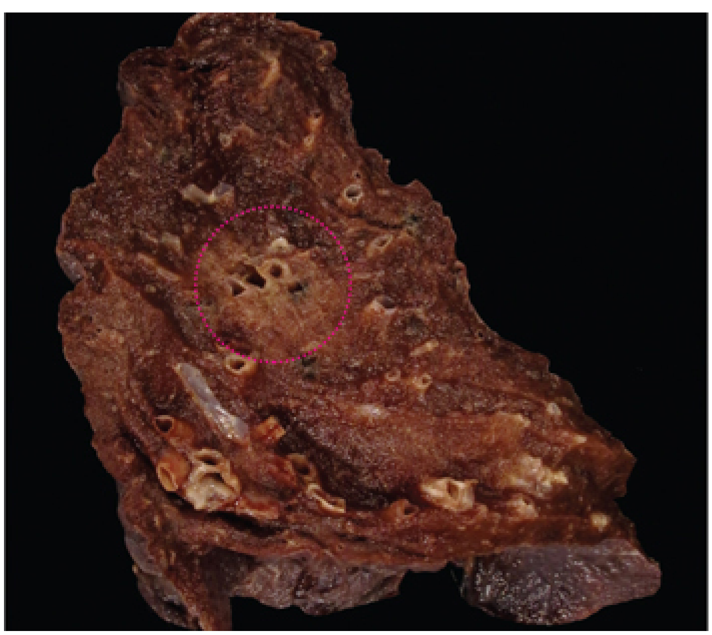

Figure 52-6. Minimally invasive adenocarcinoma (circled) in a right lower lobectomy specimen.

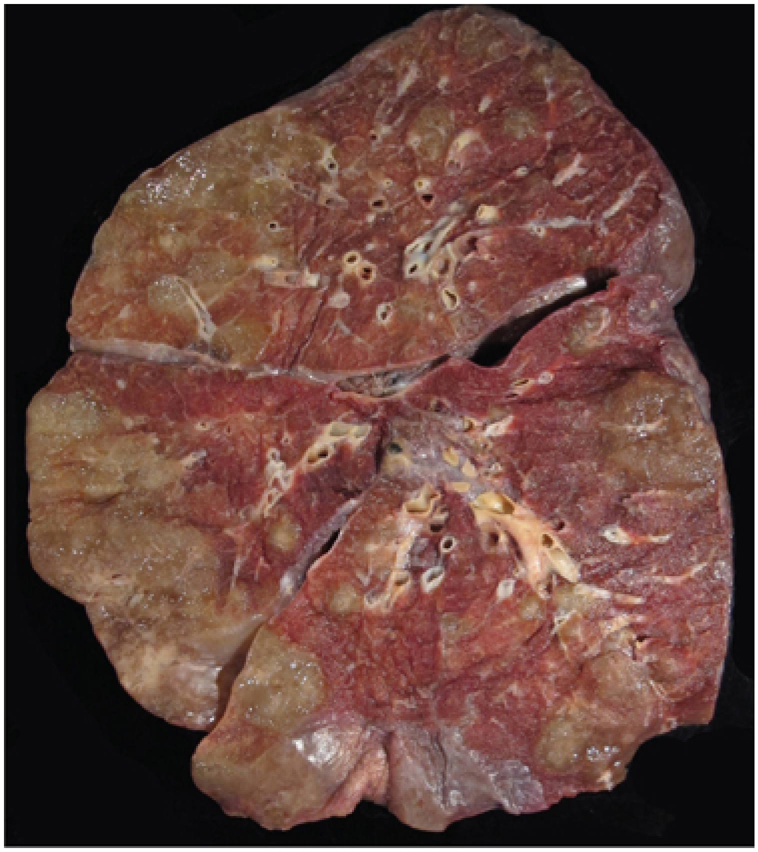

Figure-52-7. Mucinous adenocarcinoma in the right lung from an autopsy specimen.

Lastly, lymph nodes are an important component to examine in a lung resection specimen. Specific stations will often be submitted as separate specimens by the surgeon, but there are often additional peribronchial lymph nodes within the lung resection specimen that must be grossly identified and sampled. There will typically be at least a few lymph nodes within a lobectomy specimen and more within a pneumonectomy specimen. Wedge resections will occasionally contain a lymph node. The lymph nodes that may be found within lung resection specimens are generally stations 11-14 (N1 nodes). The International Association for the Study of Lung Cancer (IASLC) lymph node map for intrathoracic lymph nodes can be seen in the work by Rusch et al (2009).

III. Typical gross photos of lung resection specimens

Examples of lung resection specimens include lobectomies (see Figures 52-1 and 52-2) and wedge resections (see Figure 52-3).

The most commonly encountered histologic types of lung cancer include squamous cell carcinoma (see Figure 52-4) and adenocarcinoma (see Figures 52-5 through 52-7). Less-commonly encountered tumours include neuroendocrine tumours such as carcinoid tumour (see Figure 52-8) and neuroendocrine carcinomas (eg, small cell carcinoma).

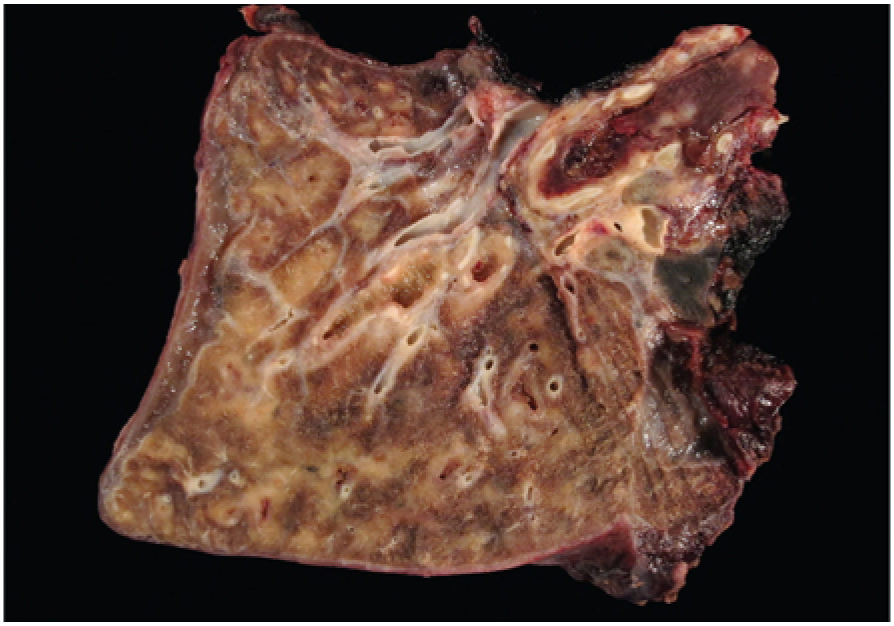

Figure 52-8. Carcinoid tumor arising within the proximal lobar bronchus in a left lower lobectomy specimen, with postobstructive changes.

Gross examination may also reveal findings in the nonneoplastic lung such as changes related to tumour obstruction (see Figure 52-9), previous treatment (see Figure 52-9), or unrelated interstitial lung disease.

Figure 52-9. Diffuse alveolar damage in a right lower lobe wedge after neoadjuvant chemo/radiotherapy. The surgeon palpated a mass lesion in the lung while performing an esophagectomy for esophageal carcinoma and took a wedge to exclude malignancy. Although the mass in this case was benign, specimens with mass lesions should be grossed in a standardized manner with gross measurement of the tumor and adequate sampling including margins.

IV. Dissection techniques: step-by-step description for a pneumonectomy specimen

1. Review relevant clinical history and chest radiography.

It is important to gather information about the specimen to help plan the dissection. One useful detail is the indication for surgery, which could include the indications mentioned in section I (in the context of neoplasia) or other nonneoplastic contexts. In scenarios where no clinical information is provided and no radiology is available for review, it is possible to gross a pneumonectomy specimen using a "one size fits all" approach or to modify the approach as pathology is revealed throughout the dissection. However, considering that infections are included in the nonneoplastic indications for lung resection or are sometimes mistaken for cancer, it is preferable to be aware of potential exposures to pathogens before handling a specimen and to consider the need for tissue culture.

Reviewing previous chest radiography is helpful in preparing for specimen dissection. Awareness of the number of lesions identified on imaging, in addition to their location, size, and relationships, allows for a focused search to identify and sample all radiologically identified abnormalities.

2. Orient the specimen.

Confirm that the specimen type matches that indicated on the specimen requisition. The right lung typically has three lobes; when looking at the hilum, its mainstem bronchus is posterior to the right pulmonary artery. The left lung typically has two lobes; when looking at the hilum, its mainstem bronchus is inferior to the left pulmonary artery. Both lungs have a narrow peak at the superior aspect, the apex, and a broad base at the inferior aspect, the diaphragmatic surface. The other surfaces are the costal and mediastinal surfaces.

3. Record the specimen weight.

4. Shave the bronchial and vascular margins.

Take shave (en face) sections of the bronchial and vascular margins at the hilum. This may require removing surgical staples, usually by trimming away the staples and a small amount of underlying tissue. If tumor approaches a stapled margin, it is preferable to remove the staples without sacrificing any lung tissue (a tedious endeavour).

If tumor is grossly visible in the airway and near the bronchial margin, a perpendicular section is preferable.

5. Sample peribronchial lymph nodes.

Any peribronchial lymph nodes visible at the hilar surface should be sampled. The lymph nodes identified at the hilar surface will likely be station 11 (between the origins of the lobar bronchi). Station 10 lymph nodes are those immediately adjacent to the mainstem bronchus and may be present in a pneumonectomy specimen, if not submitted separately by the surgeon.

6. Consider overnight inflation/fixation.

To inflate and fix the lung, it should be placed in a large container and infused with 10% neutral buffered formalin using the large airways at the hilum until the lungs appear fully expanded and the pleural surface is smooth. Be careful not to overinflate the lungs. Fill the container with formalin and allow the lung to fix overnight.

It is possible to completely perform the gross examination and dissection of the lung in the fresh state; therefore, this step can be skipped. There are advantages to this approach. One advantage is measuring tumor size in the fresh state; fixation may alter tumor size and affect tumor stage. An additional advantage is the ease of obtaining tissue for culture if infection is still in the clinical differential diagnosis or if gross findings are suggestive of infection. If procurement for cytogenetics or research purposes (“tumor banking”) is desired, it is best to obtain these samples prior to fixation.

The advantages of fixing and inflating the lung include facilitating the evaluation of the nonneoplastic lung (which would otherwise appear collapsed).

After inflation, the dimensions of the lung and each lobe should be measured in three dimensions.

7. Inspect the pleura and palpate the specimen.

The external surface of the lung should be examined and areas of abnormality identified. It is important to identify any additional tissues attached to the lung, such as parietal pleura or chest wall. Surgical margins of these structures should be inked and sampled.

Any pleural defects should be noted and inked. The lung may have been adherent to the opposing surface (eg, the chest wall). While often this is due to a pleural adhesion, it may be due to subtle tumor invasion into an adjacent structure. If the surgeon has to transect tissue, it represents a true surgical margin that needs to be evaluated microscopically.

Look for areas of pleural puckering—a finding that may indicate an underlying neoplasm. Inking areas of pleural retraction is optional. Also look for any pleural nodules, which could suggest pleural metastasis.

After external examination, palpate the specimen to see if a tumor can be identified. Is the tumor central or peripheral? What lobe or lobes are involved?

8. Dissect the specimen in a way that best demonstrates the pathology (depending on the tumor location and extent).

For centrally located tumors, bisecting the lung in the coronal plane may be the easiest way to begin. Inserting two probes into diverging airways may facilitate bisecting the lung along the desired plane.

For peripheral tumors, consider opening the airways with scissors and working distally before committing to a plane of section.

9. Describe any tumors identified.

Document the tumor size in three dimensions (to the nearest millimeter). Note the tumor location. Does it involve more than one lobe? Describe the tumor including its shape, color, texture, and consistency. Measure the distance from the tumor to all margins (ie, bronchial end, peribronchial soft tissue, vascular, and pulmonary parenchymal margin, and those of additional structures, if present) and to the visceral pleura. Describe the relationship of the tumor to airways, the surrounding lung parenchyma, the visceral pleura, blood vessels, lymph nodes, and any other tissues included in the specimen.

It is worth noting an important change in the reporting of pulmonary nonmucinous adenocarcinoma in the 8th edition of the American Joint Committee on Cancer (AJCC) pTNM staging system: only the invasive (ie, nonlepidic) component is now considered when assigning the T classification. Therefore, one should measure the size of solid tumor component(s), in addition to the size of the entire tumor (including the ill-defined noninvasive component, often difficult to distinguish from the surrounding nonneoplastic pulmonary parenchyma). As mentioned previously, awareness of imaging findings is crucial in this assessment.

If multiple nodules are present, describe each nodule as suggested above, in addition to measuring the distance between the tumors.

10. Sample tumor for light microscopy.

As a general rule, submit at least one section per centimeter of maximal tumor dimension for overtly invasive tumors; however, it is practical to submit small (less than 2 cm) tumors in their entirety, as resources allow. In addition, tumors suspected to represent either nonmucinous adenocarcinoma in situ or minimally invasive adenocarcinoma should also be submitted in their entirety, regardless of size. Sections should demonstrate the relationship of the tumor to the visceral pleura, nearby margins, and direct extension into lymph nodes or extrapulmonary structures (if present).

If the tumor has an endobronchial component, take sections along the involved airway to include both the tumor and the airway to facilitate evaluation for an in situ carcinoma component.

11. Section the remainder of the lung at 1-cm intervals.

The remaining lung parenchyma should be sectioned at 1-cm intervals to identify additional abnormalities; after sectioning, palpate each slice to help identify abnormalities that might not be easily seen.

Sample any additional abnormality identified. Submit at least one section of apparently normal lung parenchyma from each lobe.

12. Submit all peribronchial lymph nodes.

It is important to identify and submit all lymph nodes identified during the dissection. There is evidence in the literature suggesting that lung resection specimens are often inadequately sampled for lymph nodes; therefore, it is worth having a second look for lymph nodes before completing the gross examination. Identifying lymph node metastases significantly impacts patient treatment and prognosis.

To perform a focused examination for lymph nodes, attention should be paid to the tissue immediately surrounding the airways. Using blunt dissection, dissect the peribronchial tissue beginning at the bronchial resection margin and working peripherally. Lymph nodes tend to aggregate at points of airway bifurcation.

V. Gross description of pneumonectomy specimens

As described in previous chapters, Raymond's paragraph system will be used to describe the pneumonectomy specimen.

Example of gross description of pneumonectomy specimen

Specimen consists of a right lung (788 g prior to inflation, 22.0 x 21.5 x 8.0 cm after inflation) including upper lobe (17.0 x 7.5 x 7.5 cm after inflation), middle lobe (9.0 x 5.0 x 3.0 cm), and lower lobe (20.0 x 11.0 x

9.0 cm) with attached rib and muscle (10.2 x 6.5 x 2.5 cm in total, rib measuring 9.5 x 1.7 x 1.7 cm) at the upper lobe near the apex. The mainstem bronchus is patent; the vascular structures at the hilum are stapled closed.

Located in the upper lobe, there is a well-circumscribed tumor, 8.2 x 7.0 x 6.7 cm. Serial sections through the tumor show a firm tan cut surface with small friable areas. The tumor involves the upper lobe bronchus, is situated 0.6 cm from the mainstem bronchus end margin, 0.4 cm from the hilar (peribronchial) soft tissue margin, and 0.5 cm from the vascular margin. The tumor extends through the visceral pleural surface into the attached muscle but does not appear to involve the rib; tumor is within 0.2 cm of this soft tissue margin. The tumor extends to within 0.2 cm of the middle lobe but does not involve the middle or lower lobes.

Twelve lymph nodes (0.3-1.3 cm) are dissected from the lung including four between the origins of the lobar bronchi, three within the upper lobe, two within the middle lobe, and three within the lower lobe. No lymph nodes appear grossly involved by tumor.

Ink code

Black: Attached rib and muscle soft tissue margin.

Section code

A1: Mainstem bronchus margin, en face
A2: Vascular margin, en face
A3-A12: Representative sections of tumor including:
  A7: Tumor approaching mainstem bronchus margin
  A8: Tumor approaching hilar soft tissue margin
  A9: Tumor approaching middle lobe
  A10-A11: Tumor extending through pleura into muscle including closest soft tissue margin
  A12: Tumor extending near rib
A13-A14: Random sections from upper lobe away from tumor
A15-A16: Random sections from middle lobe
A17-A18: Random sections from lower lobe
A19-A22: Four station 11 lymph nodes
A23: Three upper lobe lymph nodes
A24: Two middle lobe lymph nodes
A25: Three lower lobe lymph nodes

VI. Common pathologic findings in lung resection specimens

In the majority of pulmonary resection specimens, the primary pathologic finding will be a non-small cell lung carcinoma, most commonly adenocarcinoma and less frequently squamous cell carcinoma.

In resections for a ground-glass opacity or a subsolid nodule, the primary pathologic finding may be adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA).

Small cell carcinoma is occasionally encountered as the primary pathology in lung resection specimens, but much less frequently than non-small cell carcinoma. The vast majority of patients with pulmonary small cell carcinoma present with advanced disease, beyond the stage where surgery would be considered a primary modality for treatment. In those rare presentations of small cell carcinoma with limited disease, lung resection may be performed. More commonly, however, small cell carcinoma is an unexpected finding in a lung resection specimen (ie, the clinical suspicion is non-small cell carcinoma).

Other histologic types of primary lung cancer that may be encountered include salivary gland-type tumors, carcinoid tumors, large cell neuroendocrine carcinomas, and sarcomatoid carcinomas.

As the lung is a common site for metastasis from cancers arising in other organs, pulmonary metastasis can be seen in lung resection specimens. In most cases, resection of pulmonary metastases is not part of the primary treatment for advanced cancers of other sites, although it may be done in cases of oligometastatic disease. Lung resection does not take place in most clinical scenarios involving pulmonary metastasis because there is an established clinical history of a previous malignancy and/or the radiologic findings strongly favor metastasis (ie,

numerous, bilateral lung nodules without hilar or mediastinal lymphadenopathy), which usually leads to small tissue samples (eg, biopsy) rather than resection.

Nonneoplastic disease processes may occasionally mimic malignancy based on the clinical and radiologic findings and lead to lung resection. Examples include cavitary infection, aspiration pneumonia, and parenchymal infarcts.

VII. Common potential staging pitfalls and solutions

1. Perhaps the most challenging issue for pathologists in the staging of lung cancer is determining the nature of multiple lung tumors: do they represent independent primary neoplasms or is there intrapulmonary metastatic disease? This decision is often entirely in the hands of the pathologist and is of tremendous importance to patient management. Although the identification of intrapulmonary metastases has long been a staging parameter for lung cancer, there has not been much guidance for pathologists in approaching this scenario until recent years.

The initial step is determining the histologic type of each tumor (eg, adenocarcinoma, squamous cell carcinoma); those that differ represent separate neoplastic processes (ie, synchronous or metachronous primaries). For multiple tumor nodules of the same histologic type, the distinction is more subjective because there are multiple parameters to evaluate and the weight to place on each is uncertain.

One of the most important parameters is tumor morphology: do the tumors appear similar, architecturally and cytologically? Comprehensive histologic assessment has been proposed as a method to aid in this distinction; tumors that appear different are interpreted as independent neoplasms.

Regarding lung adenocarcinomas specifically, the presence of a predominant or significant lepidic component is considered strong evidence in favor of a primary tumor.

The presence of lymphovascular invasion or lymph node metastasis suggests that intrapulmonary metastasis is more probable.

After weighing the evidence, intrapulmonary metastases within the same lobe are considered at least pT3, within a different lobe of the ipsilateral lung are considered at least pT4, and within a contralateral lobe of lung are considered at least pM1a. In cases of synchronous primaries of different histologic type, an individual TNM should be assigned to each tumor.

Lastly, in cases of multiple lung tumours, it is important to consider an extrapulmonary source. The patient's history should be reviewed to identify previously diagnosed cancers at other anatomic locations that could potentially metastasize to the lungs.

2. Tumor size

A. Formalin fixation of a lung specimen can cause a tumor to shrink and possibly alter the tumor stage. Ideally, the tumor size is measured in the fresh state; however, cutting into the tissue to obtain these measurements will limit the ability to inflate the lungs afterwards.

B. For nonmucinous adenocarcinomas with a predominant or significant lepidic component, tumor size for the purposes of tumor staging is based on the size of the invasive component only. The size measurement is at the discretion of the pathologist based on the correlation of the gross tumor size and the microscopic findings. For example, if an adenocarcinoma shows acinar pattern in the center and lepidic pattern at the periphery, a microscopic measurement of the size of the acinar pattern would be reasonable. Alternatively, if the areas of invasion are not readily measurable, invasive tumor size could be estimated by multiplying the gross tumor size by the percentage of tumor showing an invasive pattern.

3. Before considering a diagnosis of nonmucinous adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) in a lung resection specimen, the entire tumor should be submitted to exclude invasion or more extensive invasion, respectively. Tumors greater than 3.0 cm that otherwise meet the criteria for AIS or MIA should be classified as lepidic-predominant adenocarcinoma, suspect AIS or MIA, and staged as pT1a.

4. It is important to communicate with the surgeon to clarify the additional structures present in a lung resection specimen, if any (eg, mediastinal fat). Invasion into these structures can increase the pT stage.

5. Tumor invasion into an adjacent lobe, whether across the fissure or directly if the fissure is incomplete, is considered at least pT2a. As this finding may not be microscopically apparent in a histologic section, it is important to clearly describe this gross finding. There is some evidence in the literature to suggest that direct invasion across an incomplete fissure does not warrant upstaging the tumor.

6. Tumors with visceral pleural invasion are considered at least pT2a. This finding should be confirmed microscopically and requires sampling of areas where the tumor approaches the pleural surface. Evaluation is markedly facilitated by the use of elastic stains.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists.

- Describe the procedure performed and the nature of the specimen (eg, right upper lobe of lung)
- Provide the histologic type and grade.
  - For adenocarcinomas, provide the predominant growth pattern (ie, lepidic, acinar, papillary, micropapillary, or solid) and consider reporting the other patterns present and the percentage of each pattern.
  - For invasive nonmucinous adenocarcinomas with a lepidic component, provide the total tumor size (inclusive of the invasive and lepidic components) *and* the invasive tumor size.
- Is there visceral pleura invasion?
- Is the tumor limited to the lung or does it involve other structures included with the specimen?
- Where is the tumor located? Try to identify the segment, if possible. Does the tumor extend into an adjacent lobe?
- What is the status of the margins (bronchial, vascular, hilar soft tissue, lung parenchymal, other)?
- Is the tumor unifocal or multifocal? Are the additionally identified tumors synchronous primaries or intrapulmonary metastases?
- Is there lymphovascular invasion? Is there spread through air spaces (STAS)?
- How many lymph nodes were identified and how many are involved by metastasis? Is there extranodal extension?
- Did the patient receive neoadjuvant chemotherapy and/or radiation? If so, is there any treatment effect?

A sample report is provided below to demonstrate the necessary information to be included in a pathology report. Use of a synoptic template is strongly encouraged.

FINAL DIAGNOSIS:

Left lung, pneumonectomy:

- Invasive adenocarcinoma, acinar predominant, 5.5 cm in greatest dimension, located in the left upper lobe with extension into the left lower lobe.
- Resection margins (bronchial and vascular) are negative for malignancy.
- Lymphovascular invasion is identified (lymphatic).
- Twenty lymph nodes are identified; two are positive for metastatic adenocarcinoma (2/20).
- Please see the synoptic report below.

Synoptic report

The following information is a modification of the AJCC cancer staging protocol and College of American Pathologists cancer staging protocol for lung carcinoma.

Procedure: Pneumonectomy

Specimen Laterality: Left

Tumor Site: Upper lobe with extension into lower lobe

Total Tumor Size: 5.5 cm

Invasive Tumor Size: 5.5 cm

Tumor Focality: Single tumor

Histologic Type: Invasive adenocarcinoma, acinar predominant (mixed acinar [95%] and lepidic [5%] patterns)

Histologic Grade: Grade 2 (moderately differentiated)

Spread Through Air Spaces (STAS): Not identified

Visceral Pleura Invasion: Not identified

Lymphovascular Invasion: Present (lymphatic)

Direct Invasion of Adjacent Structures: Adjacent structures present but not involved

Margins: All margins are uninvolved by carcinoma (bronchial, vascular, and hilar soft tissue)

Distance of Invasive Carcinoma from Closest Margin: 2.5 cm (bronchial margin)

Treatment Effect: No known presurgical therapy

Regional Lymph Nodes:

Number of Lymph Nodes Involved: 2

Number of Lymph Nodes Examined: 20

Extranodal Extension: Not identified

Pathologic Stage Classification (pTNM, AJCC 8th Edition): pT3N1

Additional Pathologic Findings: None identified

Comments: Testing for *EGFR* mutations and *ALK* and *ROS1* gene rearrangements has been ordered and will be reported separately.

For specific definitions of current pathologic TNM staging for lung cancer, please refer to *AJCC Cancer Staging Manual,* 8th edition.

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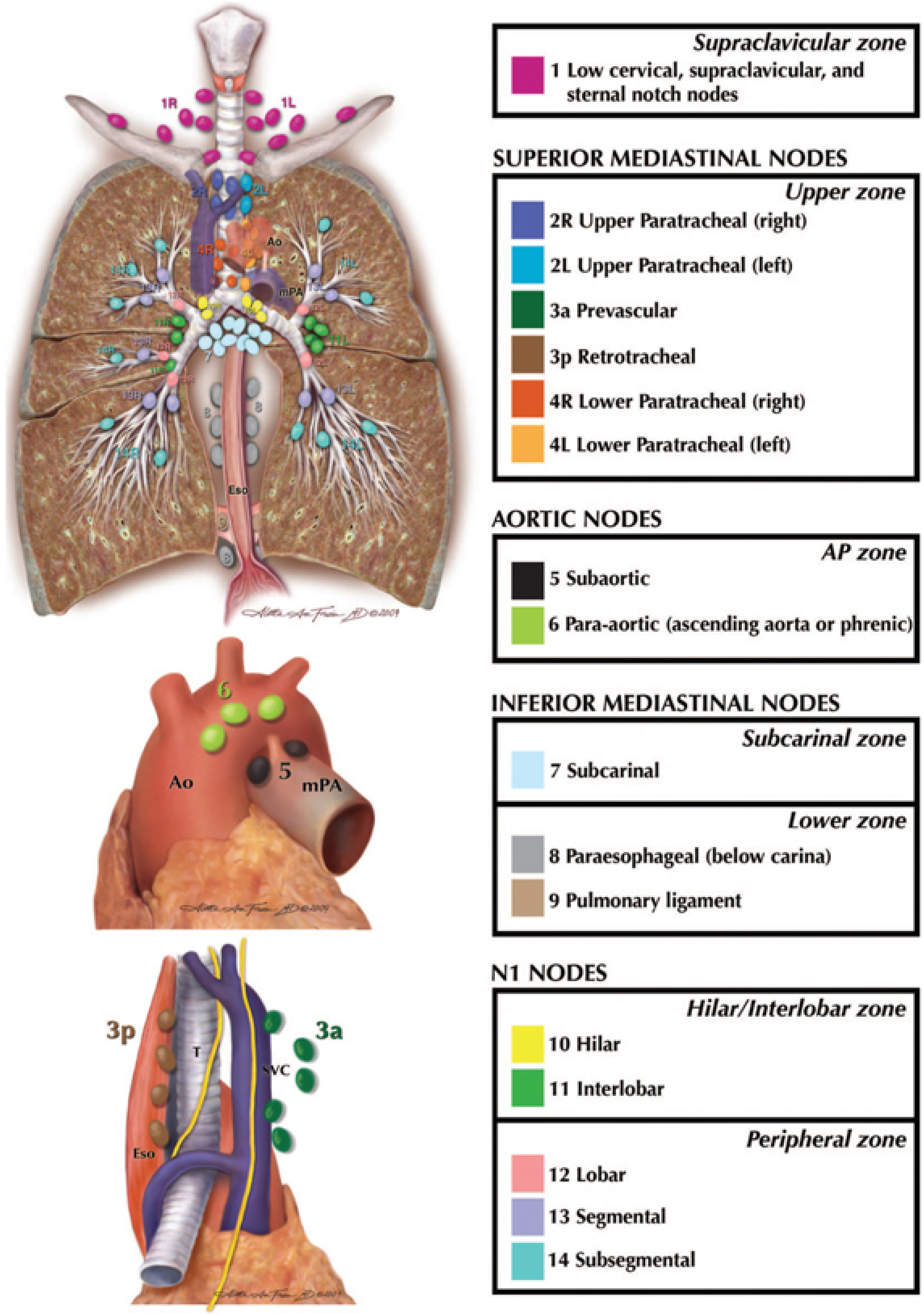

IASLC lymph node map, including the proposed grouping of lymph node stations into “zones” for the purposes of prognostic analyses.

From Rusch VW et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2009;4:568-577. Copyright Elsevier Inc. Reproduced with permission.

53. Pleural Mesothelioma

Brandon T. Larsen, MD, PhD; Mathieu C. Castonguay, MD; Paul Wawryko, MD

Malignant pleural mesothelioma (MPM) is usually diagnosed via core biopsy or incisional biopsy material and occasionally on cytology preparations of pleural fluid. Surgical resections for MPM are uncommon but may be attempted when the clinical and imaging studies show either surgically resectable or potentially surgically resectable disease, in the hopes that a surgical cure might be achieved. Specimens usually consist of an entire lung with en bloc removal of the parietal pleura and adjacent portions of the diaphragm and parietal pericardium ("extrapleural pneumonectomy") and occasionally also include other attached tissues. Infrequently, lesser resections may be performed for palliative reasons without intent to cure, and these will only be briefly mentioned in this chapter, with the primary focus placed on the extrapleural pneumonectomy specimen.

Although the anatomy of extrapleural pneumonectomy specimens is often complex, gross examination can generally be performed using the same principles that guide dissection of conventional pneumonectomy specimens for lung cancer that include en bloc resection of additional structures, as outlined in the pulmonary resection chapter. These principles will only be briefly reiterated here, with specific emphasis placed on aspects relevant to MPM diagnosis and staging, and the reader is referred to the pulmonary resection chapter for a more detailed discussion of general aspects. Like any oncologic resection, proper gross examination and handling of the extrapleural pneumonectomy specimen is critical for accurate staging and selection of appropriate therapy, and the need for a succinct and well-organized pathology report cannot be overemphasized.

I. Indications for resection of MPM

1. Extrapleural pneumonectomy

Extrapleural pneumonectomy is generally performed when the intent is surgical cure and is generally reserved for patients with surgically resectable or potentially surgically resectable disease. Depending on the extent of disease, en bloc resection of additional adjacent involved tissues may also be performed.

2. Pleurectomy/decortication

This procedure may occasionally be performed with an intent to cure (such as in a rare case of localized malignant mesothelioma) but is usually performed as a palliative procedure to improve breathing, control pleural effusions, and/or control pain.

3. Partial pleurectomy/debulking

As with pleurectomy and decortication, these procedures are usually employed as a palliative measure for the same reasons and are not typically performed with curative intent.

II. What do we expect to see in an MPM resection specimen macroscopically and microscopically?

In general, MPM spreads diffusely across the pleural surfaces, and the macroscopic features will depend on the extent of disease; this ranges from minimal pleural thickening to multiple nodular deposits and even diffuse rind-like thickening around the lung and along the fissures, with fusion of the visceral and parietal pleurae (Figure 53-1). Although there is often diffuse and relatively uniform pleural thickening, in some cases the deposits are more discontinuous or irregular and can even invade the lung, chest wall, or other structures and form large bulky tumors.

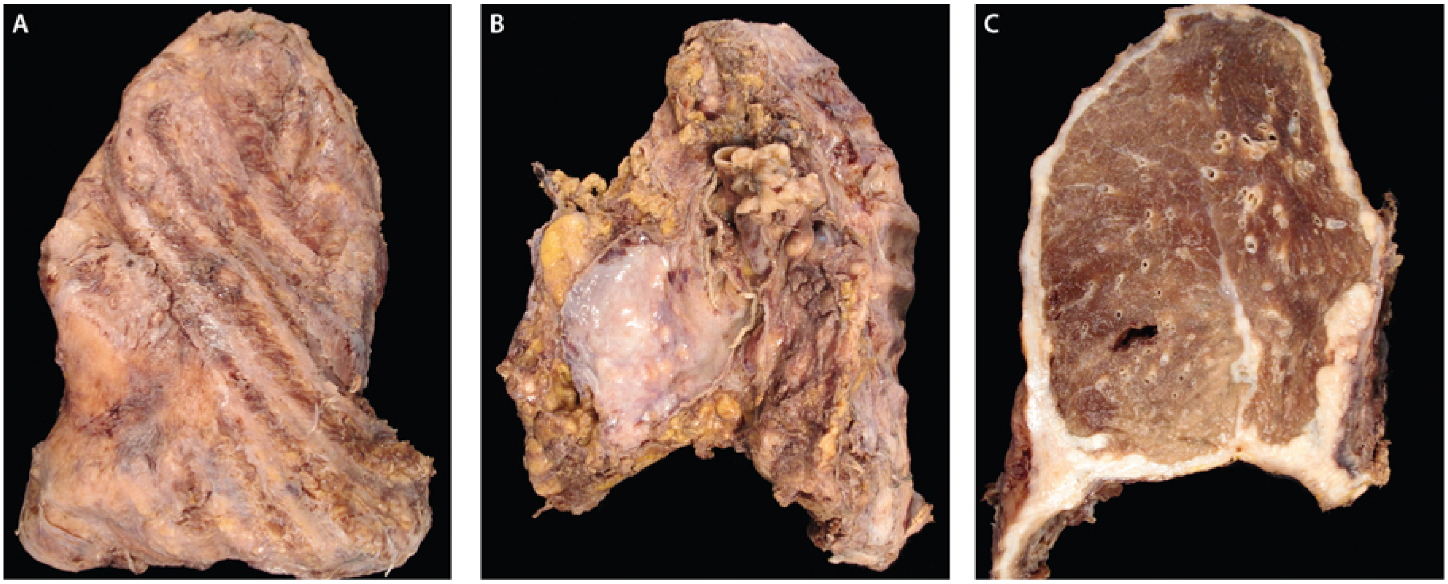

Figure 53-1. Gross photographs of an extrapleural pneumonectomy specimen, seen from the lateral (A) and medial (B) aspects and in a coronal cross-section (C). Note the resected portions of diaphragm and parietal pericardium that accompany this en bloc resection of the right lung.

It should be remembered that pathologic tumor staging of MPM is dependent on both disease extent and surgical resectability, and careful gross examination is critical for determining these features. As with any oncologic resection, correlation with imaging and intraoperative findings or direct discussions with the surgeon can be invaluable to guide the gross examination and proper submission of sections, especially those of clinical or intraoperative interest, to achieve accurate staging. It should be remembered that assessment of the relationship of the tumor to the endothoracic fascia is difficult for pathologists to appreciate grossly and histologically, and is best made by the surgeon intraoperatively; the pathologist should have a low threshold for discussing these challenging specimens with the surgeon.

As with lung carcinomas, the status of regional lymph nodes is an important component of staging, and gross examination should always include submission of the regional lymph nodes. In general, the nodal staging system follows the lymph node map for lung tumors. However, it should be remembered that the lymphatic drainage of the pleura is different from that of the lung parenchyma, and that patterns of nodal involvement in early-stage MPM may be different than those typically seen with lung cancers: early metastases often involve the internal mammary, peridiaphragmatic, pericardial fat pad, and posterior intercostal lymph nodes. Consequently, specific attention should be paid to these more unusual nodal stations when examining an extrapleural pneumonectomy specimen with MPM.

IV. Dissection techniques: step-by-step description for an extrapleural pneumonectomy specimen

1. Review clinical information and chest radiography. When extrapleural pneumonectomy is performed, it is with intent to cure because the clinical and imaging findings suggested that the disease was at least potentially surgically resectable. Consequently, a major goal of pathologic examination is to address completeness of surgical resection. Awareness of any potential areas of unresectable disease, either on preoperative imaging studies or intraoperatively, is valuable for adequate evaluation in the surgical pathology laboratory. Reviewing preoperative imaging studies is also helpful to ensure proper specimen orientation. Review of the operative note or direct discussion with the surgeon will help to clarify the nature of additional attached structures and margins, the relationship of the tumor to the endothoracic fascia (as seen intraoperatively), and other areas of concern to the surgeon.

2. Specimen orientation. The anatomy of extrapleural pneumonectomy specimens can be complex, especially when additional adjacent involved tissues have been removed en bloc. If specimen orientation or the nature of attached tissues is unclear, clarification with the surgeon is essential.

3. Record the specimen weight.

4. Shave and submit the bronchial and vascular margins. These margins can be handled using the same principles that are outlined in the chapter on lung tumor resections.

5. Sample hilar and peribronchial lymph nodes.

6. Ink the relevant surgical margins. Unlike a conventional pneumonectomy specimen, an extrapleural pneumonectomy specimen is surrounded on all sides by a true margin (unless otherwise specified by the surgeon). If other attached tissues are also present (eg, a portion of chest wall), there may also be other margins that require evaluation.

7. Consider overnight inflation/fixation. This can be performed in a fashion similar to the procedure described in the pulmonary resection chapter.

8. Dissect the specimen in a fashion that best demonstrates the location and extent of disease. In some cases, it may be helpful to section through this specimen in the axial plane, as this will generally correlate well with the CT scan. In other cases, it may be more helpful to section the specimen in the saggital plane, as is commonly performed in autopsy evaluation of the lungs. Occasionally, other dissection methods will be required to address specific clinical questions or surgeon concerns.

9. Describe and document the extent of disease. Specific attention should be paid to involvement of the diaphragm, underlying pulmonary parenchyma, parietal pericardium, and other attached structures. In addition, special attention should be paid to the relationship of the tumor to each margin, as the surgical resectability of disease is an important component of pathologic tumor staging.

10. Submit representative sections of tumor. In particular, take sections to demonstrate the relationship of the tumor to the diaphragm, parietal pericardium, underlying pulmonary parenchyma, and other attached tissues, as well as other areas of concern.

11. Submit representative sections of the background lung and other nonneoplastic abnormalities. Although the gross appearance of MPM can be quite dramatic and can easily capture the attention of the pathologist or pathology assistant, evaluation of the background pulmonary parenchyma should not be neglected. MPM is not the only disorder that is associated with asbestos exposure, and evaluation for asbestos-related interstitial lung disease ("asbestosis") is an important component of the comprehensive pathologic evaluation of the extrapleural pneumonectomy specimen. As with any interstitial lung disease, proper evaluation should include submission of sections from each lobe, preferentially from areas that are only moderately abnormal, and avoiding areas of end-stage fibrosis and honeycombing. If fibrous or calcified pleural plaques are present, these should also be sampled as they are an important clue that strongly suggests asbestos exposure.

12. Consider having a second look for lymph nodes. It is important to identify and submit all lymph nodes identified during the dissection. It is also important to remember that nodal metastasis may preferentially involve lymph nodes in locations that would be unusual for metastatic lung cancers, such as internal mammary, peridiaphragmatic, pericardial fat pad, and posterior intercostal lymph nodes. A careful search for these lymph node stations should be performed in addition to a routine dissection for hilar and peribronchial lymph nodes.

V. Gross descriptions using paragraph system

As described in previous chapters, Raymond's paragraph system will be used to describe the extrapleural pneumonectomy specimen.

Example of gross description of extrapleural pneumonectomy specimen with MPM

Received in formalin is an extrapleural pneumonectomy specimen, composed of an en bloc resection of right lung (852 g prior to inflation, 23.0 x 21.5 x 8.5 cm after inflation) with parietal pleura and portions of diaphragm (10.7 x 5.7 x 1.0 cm) and parietal pericardium (8.4 x 7.2 x 0.6 cm). The margins are inked black.

Sectioning reveals diffuse "rind-like" thickening of the pleural surface, with encasement of the lung and extension into fissures, including numerous solid tan pleural tumors (0.7-2.5 cm in greatest dimension). Tumor does not extend into the hilum or mediastinal fat, and the bronchial and vascular margins are uninvolved by tumor (by 1.7 cm and 1.5 cm, respectively). Tumor measures less than 1 mm from the peripheral margin on the

lateral surfaces of the upper and lower lobes, but per the surgeon the tumor did not invade the endothoracic fascia of the chest wall in these areas.

Tumor focally invades the diaphragm but does not extend to the peritoneal surface, and the peripheral diaphragmatic margins are uninvolved (nearest peripheral diaphragmatic margin 0.6 cm from tumor, at the lateral aspect). Tumor also focally invades the parietal pericardium but does not extend to the inner pericardial surface, and the peripheral pericardial margins are uninvolved (nearest peripheral pericardial margin 0.9 cm from tumor, at the inferior aspect). No intrapulmonary growth is seen, but the lung shows patchy and peripherally accentuated fibrotic changes with subpleural honeycombing in all three lobes, suspicious for interstitial lung disease. Lastly, plate-like calcification of the pleura is present over a 3.5 x 2.5 cm area adjacent to the diaphragm, suspicious for an old calcified pleural plaque.

Fifteen lymph nodes (0.3-1.3 cm) are identified (10 peribronchial, 3 hilar, and 2 peridiaphragmatic). No lymph nodes appear grossly involved by tumor.

Section code

A1: Mainstem bronchus margin, en face
A2: Vascular margin, en face
A3-A8: Tumor to nearest peripheral margins, including:
- A3: lateral RUL
- A4: lateral RLL
- A5: anterior RML
- A6: medial RUL
- A7: medial RLL
- A8: posterior RLL

A9: Tumor to lung, RUL
A10: Tumor to lung, RML
A11: Tumor to lung, RLL
A12-A13: Tumor to diaphragm
A14: Tumor to nearest peripheral diaphragmatic margin
A15-A16: Tumor to parietal pericardium
A17: Tumor to nearest peripheral pericardial margin
A18: Uninvolved lung with fibrosis, RUL
A19: Uninvolved lung with fibrosis, RML
A20: Uninvolved lung with fibrosis, RLL
A21: Possible old calcified pleural plaque, submitted after decalcification
A22: Four peribronchial lymph nodes
A23: Three peribronchial lymph nodes
A24: Three peribronchial lymph nodes
A25: Three hilar lymph nodes
A26: Two peridiaphragmatic lymph nodes

VI. Common pathologic findings in extrapleural pneumonectomy specimens

Although MPM is an uncommon tumor, most extrapleural pneumonectomy procedures are performed to treat this tumor. Hence, MPM is the most common finding in the extrapleural pneumonectomy specimen. Often, old calcified fibrous pleural plaques are also present.

It should be remembered that interstitial lung disease can also be present. Although the dramatic presentation of MPM grossly and histologically can capture much of one's attention, care must be taken to ensure that the lung parenchyma itself is also appropriately evaluated for interstitial disease (especially asbestosis), as well as other common lung diseases (eg, emphysema). The presence of intrinsic parenchymal disease may have important postsurgical implications for the patient with only one remaining lung.

Rarely, extrapleural pneumonectomy has been performed as a treatment for other pleural-based tumors (eg, synovial sarcoma). Further discussion is beyond the scope of this review, but a similar approach to specimen handling is generally utilized.

VII. Common potential staging pitfalls and solutions

As with any tumor resection, involvement of margins of the extrapleural pneumonectomy specimen has staging, prognostic, and potential therapeutic implications. Specimen orientation is usually straightforward, but identification of areas of intraoperative concern (eg, a margin worrisome for invasion of the endothoracic fascia) may be difficult if not impossible at the grossing bench without direct communication between the surgeon and pathology staff. Proper gross examination and tissue sampling from areas of interest is essential, and the pathologist and/or pathology assistant should ensure that this communication occurs as part of specimen handling.

As already stated in previous sections, it is important to remember that the pattern of lymph node metastasis in MPM can differ from the typical pattern of lymph node metastasis occurring with lung carcinomas, because of the different lymphatic drainage from the pleura. Unusual lymph node stations can be preferentially involved by metastatic MPM, such as the internal mammary, peridiaphragmatic, pericardial fat pad, and posterior intercostal lymph nodes, even when other mediastinal lymph node stations are uninvolved. Consequently, a careful search for lymph nodes in these unusual stations should also be performed in addition to a routine dissection for hilar and peribronchial lymph nodes.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged.

Information provided should include the specimen type, laterality, specimen integrity, procedure performed, tumor site and focality, histologic tumor type, tumor extension into adjacent structures or organs, margin status, the effect of neoadjuvant therapy, lymph node status, and pathologic stage classification; optional data elements include any additional findings, ancillary testing, clinical history, and tumor size in cases of localized malignant mesothelioma.

An example of a surgical pathology report is provided below.

FINAL DIAGNOSIS:

Lung and parietal pleura, right, extrapleural pneumonectomy with en bloc partial resection of diaphragm and parietal pericardium:

- Diffuse malignant mesothelioma, biphasic type (see synoptic report).

Synoptic report

Specimen: Lung, parietal pleura, diaphragm, and parietal pericardium

Procedure: Extrapleural pneumonectomy with en bloc partial resection of diaphragm and parietal pericardium

Specimen Integrity: Intact

Specimen Laterality: Right

Tumor Site: Visceral and parietal pleurae

Tumor Focality: Diffuse

Histologic Type: Diffuse malignant mesothelioma, biphasic type

Tumor Extension: Confluent visceral and parietal pleural tumor, with focal superficial extension into diaphragm and parietal pericardium but without extension to peritoneal or pericardial surfaces

Margins: All margins negative for mesothelioma

Treatment Effect: Not applicable (no neoadjuvant therapy)

Pathologic Stage Classification (pTNM, AJCC 8th Edition):

Primary Tumor (pT): pT3

Regional Lymph Nodes: pN0

Number of lymph nodes involved: 0

Number of lymph nodes examined: 15

Distant Metastasis (pM): Not applicable

Additional Pathologic Findings: One old calcified fibrous pleural plaque

Ancillary Studies:

Immunohistochemistry shows positive staining of the tumor cells for CK5/6, calretinin, WT-1, and D2-40, without staining for MOC-31, polyclonal CEA, BerEP4, CD15, or TTF-1, further supporting the diagnosis.

The above information is a modification of the American Joint Committee on Cancer (AJCC) cancer staging protocol and College of American Pathologists (CAP) cancer staging protocol for pleural mesothelioma.

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54. Thymus

Mathieu C. Castonguay, MD; Paul Wawryko, MD; Brandon T. Larsen, MD, PhD

Introduction

Surgical treatment of thymic neoplasms includes complete thymectomy and extended thymectomy (ie, with the additional removal of contiguous mediastinal adipose tissue, right and left mediastinal pleura, and aortico-pulmonary window tissue). The surgical approach can be either open (ie, via sternotomy) or minimally invasive. While transcutaneous needle core biopsy is feasible to establish the diagnosis prior to resection, this is not always performed, depending on clinical and imaging features; furthermore, definitive classification of thymomas is best reserved for resection specimens, given the likelihood for sampling error with a small biopsy and the mixed histologic patterns that are often seen.

Complete surgical resection is associated with the best outcomes for patients with thymic epithelial neoplasms. Pathologic examination of resected tumors is the gold standard tor classification and staging of these neoplasms, which provides valuable prognostic and therapeutic information. Proper handling of these specimens requires collaboration between the surgical and pathology teams, and provides the basis for accurate reporting. In this chapter, we will discuss appropriate specimen handling, microscopic evaluation, and the pertinent information to include in the pathology report.

While multiple staging systems have been proposed over the past four decades, the 8th edition of the TNM classification is the first developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) applicable to all types of thymic epithelial neoplasms, as proposed in collaboration by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG).

I. Indications for thymectomy

1. For resection of a radiographically detected thymic tumor, usually without preceding treatment with chemotherapy or radiation therapy (this category will be the primary focus of the remainder of this chapter)
2. For management of certain immunological disorders (eg, myasthenia gravis) in patients without an associated thymic tumor
3. To allow for adequate surgical exposure of retrothymic structures during nonthymic procedures (eg, pediatric cardiac surgery)

II. What do we expect to see in the thymectomy specimen?

In patients who undergo resection for evaluation of a thymic tumor, gross examination of the thymectomy specimen should include not only description of the tumor of interest, but also document the presence of additional tissues (eg, parietal pericardium, lung) included in the resection specimen and their relationship to the tumor, and the integrity of the specimen.

For optimal evaluation, close communication between the surgeon and pathology personnel is essential, especially regarding specimen components, its orientation, and areas of particular concern (eg, suspected close margin(s) and areas of specimen disruption). The use of a "mediastinal board" is advocated by the ITMIG to facilitate orientation (see Figure 54-1).

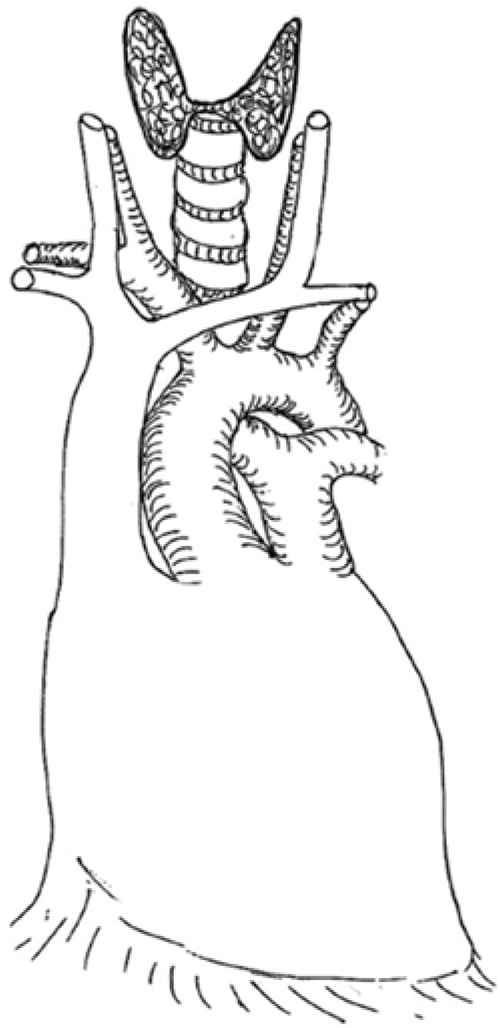

Figure 54-1. Mediastinal board. A diagram on a soft board is useful in maintaining proper dimensions and orientation of specimens.

From Detterbeck FC et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol.* 2011;6(7 Suppl 3):S1730-S1738. Copyright Elsevier Inc. Reproduced with permission.

III. Typical macroscopic appearance of thymectomy specimens

Thymic epithelial neoplasms are rare tumors; amongst these, thymomas are most common, followed by thymic carcinomas and neuroendocrine tumors. Although these tumors are considerably heterogeneous, the gross features allow for reasonably accurate prediction of tumor type (see Figure 54-2). Thymomas are usually well circumscribed, at least partially encapsulated, and lobulated (with the exception of type A thymomas); cystic change, necrosis, and hemorrhage are variable features. Thymic carcinomas are usually larger, unencapsulated, and obviously invasive, with areas of necrosis and hemorrhage, and without the lobulation seen in thymomas. Thymic neuroendocrine tumors are unencapsulated and poorly lobulated, and range from well circumscribed to frankly invasive.

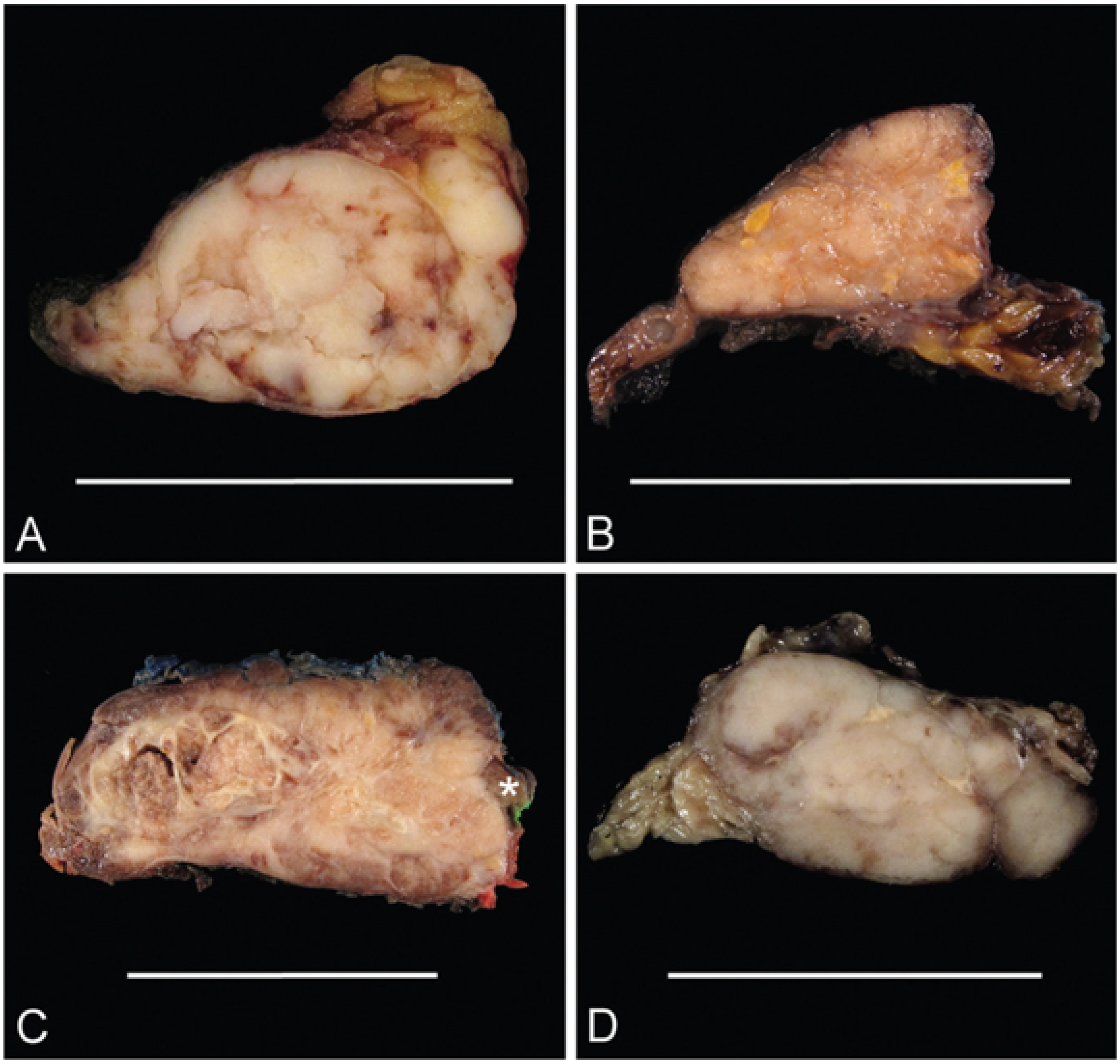

Figure 54-2. A. Thymoma (type B1), with extracapsular invasion. B. Thymoma (type B3), with foci of necrosis. C. Thymoma (type B2 and B3), with adherent lung tissue (*). D. Thymic carcinoid tumour (scale, 5.0 cm).

Thymic epithelial neoplasms often show considerable intratumoral heterogeneity microscopically (see Figure 54-3). Therefore, at a minimum, histologic sampling should include one tissue block for each centimeter of maximal tumor dimension.

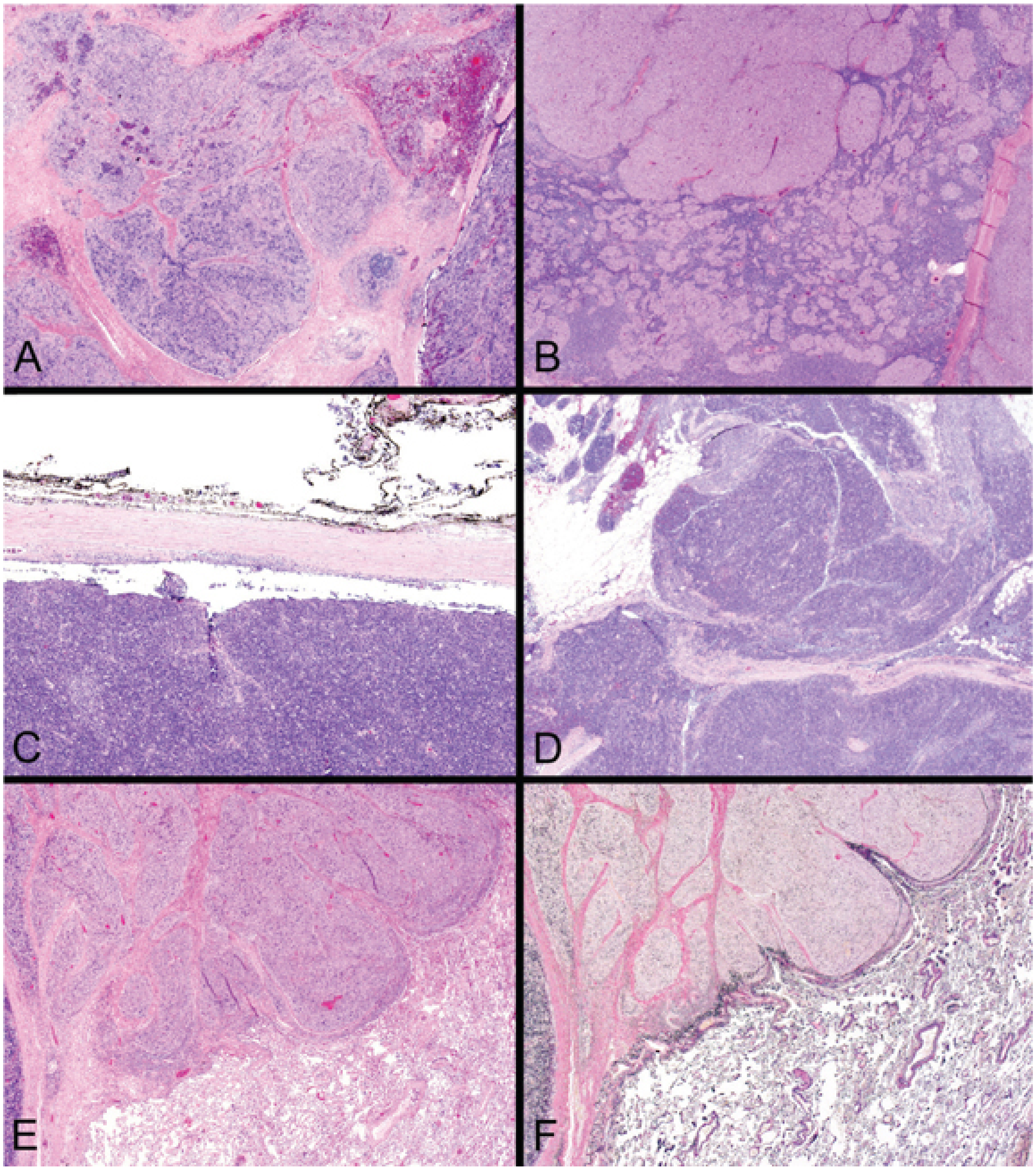

Figure 54-3. A. Thymoma, type B2 (H&E, original magnification x20). B. Thymoma, including micronodular thymoma with lymphoid stroma and type A components (H&E, original magnification x20). C. Thymoma, type B1, with intact capsule (H&E, original magnification x40). D. Thymoma, type B1, with transcapsular invasion (H&E, original magnification x20). E, F. Thymoma, type B3 , with pulmonary invasion (E, H&E, original magnification x20; F, elastic, original magnification x20).

IV. Dissection technique of thymectomy specimens

1. Review relevant clinical and imaging information

- As for any oncologic surgical resection specimen, awareness of pertinent preoperative features, such as the age of the patient, symptoms attributed to the tumor, neoadjuvant treatment, number and size of tumors, and relationship of tumor to other mediastinal structures, will help avoid potential discrepancies.

2. Orient the specimen

- Orientation of thymectomy specimens can be quite challenging and is simplified through close collaboration with the surgeon, using sutures, sketches, and/or digital specimen photographs; as mentioned previously, the ITMIG advocates for the use of a mediastinal board (similar to the "neck board" used in head and neck surgery) to secure the oriented specimen (see Figure 54-1).

3. Record the specimen weight and dimensions.

4. Using indelible ink of different colors, mark the specimen margins (anterior, posterior, right, and left, in addition to those of adjacent structures (if present).

5. Serially section the tumor in thin sections, preferably in the transverse plane.

6. Describe the tumor, including its:

- Size in three dimensions, to the nearest millimeter
- Location, and relationship to margins and to other structures (if present)
- Circumscription, encapsulation, lobulation, uniformity, color, consistency, necrosis, cystic change, hemorrhage

7. Submit fresh tumor tissue for evaluation by flow cytometry and cytogenetics; these modalities are useful for evaluation of hematopoietic neoplasms, which feature prominently in the differential diagnosis of thymic tumors.

8. Bank fresh tissue for research (if applicable), following the institutional guidelines, if a research protocol is available.

9. Allow the specimen to fix overnight, most commonly in 10% neutral-buffered formalin.

10. Submit representative sections of tumor for light microscopy, including its relationship to margins and to other structures (if present); one should submit at least one section per centimeter of tumor, given the potential for microscopic heterogeneity in thymomas (the ITMIG recommends sampling at least five representative sections, regardless of tumor diameter); small tumors can be submitted in their entirety.

11. Serially section the remainder of the specimen, and examine for the presence of additional lesions and lymph nodes (these should be individually measured)

12. Submit representative sections of nontumoral thymus and all possible lymph nodes

V. Gross description of thymectomy specimens using paragraph system

As described in other chapters, Raymond's paragraph system will be used to describe the thymectomy specimen.

Example of gross description of thymectomy specimen with tumor

Received fresh, labeled "thymus and pericardium," is a thymectomy specimen (15.0 x 12.1 x 6.2 cm; 95 g); as indicated by the surgeon, a long suture indicates the right upper pole and a short suture the left lower pole, and a portion of parietal pericardium (4.9 x 4.5 x 1.1 cm) adheres to the left lateral aspect of the specimen.

There is a single, well-circumscribed, partially encapsulated, lobulated, firm, tan-to-gray thymic tumor (5.2 x 4.6 x 3.2 cm), which appears to invade the pericardium (without involving its surface) and extends to 0.1 cm of the posterior perithymic resection margin, 0.7 cm of the right perithymic margin, 0.9 cm of the left perithymic margin, 1.2 cm of the anterior perithymic margin, and 1.4 cm of the pericardial radial margin; there is no apparent tumor necrosis or hemorrhage.

There are three possible lymph nodes (from 0.2 to 0.4 cm) in the surrounding mediastinal adipose tissue. There are no additional apparent abnormalities. The tumor is photographed.

Ink code

Anterior margin: blue

Posterior margin: black

Right margin: yellow

Left margin: orange

Circumferential pericardial margin: red

Section code

A1: Tumor with anterior margin

A2: Tumor with right margin

A3: Tumor with left margin

A4-A6: Tumor with posterior margin

A7, A8: Tumor with pericardium (including its margin)

A9, A10: Nontumoral thymus

VI. Common pathologic findings in thymectomy specimens

Although thymoma is a rare tumor, it is the most common mediastinal tumor in adults and hence is the most likely finding in thymectomy specimens.

While there exist several systems for the histologic classification of the various types of thymomas and thymic carcinomas, the World Health Organization (WHO) classification system (whose 4th edition was published in 2015) is most commonly used. The WHO classification system also applies to thymic neuroendocrine tumors.

A variety of additional neoplastic and nonneoplastic conditions may be present in thymectomy specimens, either incidentally or as the indication for resection. A detailed review is beyond the scope of this text.

VII. Common potential staging pitfalls and solutions

Specimen orientation can be difficult unless performed in close collaboration with the surgeon. Specifically, alerting the pathology personnel of the location of extrathymic tissues (including mediastinal pleura, parietal pericardium, lung, and phrenic nerve, among others) will ensure that these are appropriately inked and sampled during laboratory dissection. Involvement of these structures has a direct impact on tumor staging.

One should note that the mediastinal pleura is difficult to define histologically. The ITMIG has proposed that a discontinuous elastin layer serve as the histologic boundary of the mediastinal pleura, which can be highlighted by elastic tissue stains. Similarly, parietal pericardial involvement requires invasion of its fibrous layer and not solely of pericardial adipose tissue.

There are several pitfalls regarding the reporting of resection margins in thymectomy specimens:

- Thymic tumors are often surrounded by only a thin layer of loose connective tissue, which is easily disrupted during handling in the laboratory; careful inking and sectioning can minimize the risk of over-reporting margin involvement by tumor.
- It can be difficult to distinguish normal from neoplastic thymus, especially in cases of B1 thymoma and in those where a small amount of normal thymic tissue has been resected outside the capsule of a thymoma; in general, the lobules of B1 thymoma are of variable size and separated by fibrous septa, with more prominent cortical areas rather than medullary islands, in distinction from normal (or even hyperplastic) thymus.
- Areas of specimen disruption pose a particular challenge. Unless indicated by the surgeon, these risk being interpreted as involved margins by laboratory personnel, especially following formalin fixation and tissue retraction.

Distinguishing lymph node from thymic tissue can be challenging in some cases; paying close attention to architectural features of normal lymph nodes (fibrous capsule, cortical, paracortical, and medullary areas, with subcapsular and medullary sinuses) resolves the issue in most cases while, in others, immunohistochemical studies will help to confirm the absence of (nonneoplastic) epithelial cells in lymph nodes.

In previous staging systems, capsular invasion by tumor was of particular importance; however, this feature was difficult to evaluate in the many thymomas that are incompletely encapsulated. Although still included as a required data element in the synoptic reporting of thymomas, capsular invasion is of little clinical significance and does not factor into the TNM staging classification.

VIII. What to include in the pathology report

The final pathology report should include critical information listed by priority, although the reporting style may vary among practicing pathologists. The use of synoptic reporting is encouraged where available.

Information provided should include the procedure performed, the tumor size, histologic tumor type, presence or absence of transcapsular invasion (for thymomas only), tumor extension into adjacent structures or organs, the status of resection margins, the effect of neoadjuvant therapy, lymphovascular invasion, status of regional lymph nodes, and pathologic stage classification; optional reportable data elements include the

modified Masaoka stage (for thymomas only), the presence of additional pathologic findings, the results of ancillary studies, and case comments.

An example of a surgical pathology report is provided below.

FINAL DIAGNOSIS:

Thymus, thymectomy and partial pericardiectomy:

- Thymoma, type B2, pT2N0 (see synoptic report)

Synoptic report

Procedure: Thymectomy and partial pericardiectomy

Tumor size: 5.2 cm

Histologic type: Type B2 thymoma

Transcapsular Invasion: Present

Tumor Extension: Tumor invades pericardium

Margins: Uninvolved by tumor (distance to closest margin [posterior], 1 mm)

Treatment Effect: No known presurgical therapy

Lymphovascular invasion: Not identified

Regional Lymph Nodes:

  Number of lymph nodes involved: 0

  Number of lymph nodes examined: 3

Pathologic Stage Classification (pTNM, AJCC 8th edition): pT2N0

Additional Pathologic Findings: Age-appropriate involution changes; follicular thymic hyperplasia

Ancillary Studies: Immunohistochemical studies reveal that the neoplastic epithelial cells are reactive to antibodies directed against CK AE1/AE3, p40, and PAX8, and that the admixed lymphocytes include predominantly immature (CD3- and TdT-reactive) T cells.

The above information is a modification of the AJCC cancer staging protocol and College of American Pathologists cancer staging protocol for thymic tumors.

For specific details of pathologic TNM staging for thymic tumors, please refer to the *AJCC Cancer Staging Manual*, 8th edition.

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